Summary of Research Activities by Key Approach and Resource

Clinical and Translational Research

The obesity epidemic combined with an aging population has made diabetes the most common cause of kidney failure, nontraumatic lower limb amputation, and new cases of blindness among working-age Americans. Diabetes also is a leading cause of heart disease and stroke. Nearly 11 percent of American adults 20 years and older have diabetes and 57 million have pre-diabetes—elevated blood sugar levels not yet in the diabetic range. African Americans, Hispanic/Latino Americans, American Indians, Asian Americans, and Pacific Islanders are at particularly high risk. Globally, more than 180 million people have diabetes, and the number is likely to more than double by 2030.

The landmark NIH-supported Diabetes Prevention Program (DPP) clinical trial sought ways to prevent type 2 diabetes and found that a lifestyle intervention—reduced dietary fat and calories, moderate exercise, and a goal of a 7 percent reduction in body weight—lowered the risk of developing type 2 diabetes by 58 percent. Study participants receiving the drug metformin along with standard medical advice about diet and exercise had a 31 percent lower risk than those receiving standard medical advice alone. The interventions worked in all ethnic and racial groups studied, in both men and women, and in women with a history of gestational diabetes. The DPP Outcomes Study continues to follow most of the participants to evaluate the lasting benefits of the interventions. The critical challenge today is to move this proven program into widespread use. NIH is supporting translational research to find better methods for identifying people with pre-diabetes and to develop cost-effective ways of implementing the DPP-based lifestyle intervention. One successful program is delivering a lifestyle intervention based on the DPP in a group setting at YMCAs.

Introduction

As the steward of medical and behavioral research for the Nation, NIH is supporting scientific research in pursuit of fundamental knowledge about the nature and behavior of living systems and the mechanisms of disease. Achieving this mission requires a research continuum from basic discovery to accelerated translation of biomedical discoveries into clinical and community practice, with feedback loops at every step (Figure 1). In this report, clinical and translational research are considered together because the two areas overlap, with translational efforts often focusing on dismantling barriers that slow the progress of clinical research or impede the adoption of new and effective interventions.
1. The research continuum begins with **basic research**—the study of the fundamental mechanisms of disease and behavior. Basic research is a major force for progress in the biomedical and behavioral sciences and can lead to insights essential to understanding basic human biology and behavior in both normal and diseased states. Basic research is thus a critical component of the Nation’s public investment in research and a central feature of NIH’s research program. (Also see the section on Molecular Biology and Basic Sciences in Chapter 3.)

2. NIH is a key supporter of **early (or preclinical) translational research**—studies that serve as a bridge between basic science and human medicine. The early translational stage applies fundamental laboratory discoveries to the preclinical development of studies in humans. Such early translational investigations often are carried out using animal models, cultures, samples of human or animal cells, or a variety of experimental systems such as computer-assisted modeling of disease progression and drug therapy.

3. **Clinical research** is patient-oriented research that is conducted with human subjects (that is, studies that involve direct interaction between investigators and human subjects or the use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject). Clinical research includes clinical trials, behavioral and observational studies (also see the section on Epidemiological and Longitudinal Studies in Chapter 3), outcomes and health services research, as well as the testing and refinement of new technologies. Investigations that use only anonymous specimens or other “de-identified” data from human subjects, however, are excluded from the umbrella of clinical research. Such studies would likely fall into the categories of basic or early translational research.

Clinical trials, a crucial subset of clinical research, are the best method of determining whether interventions are safe and effective in people and assessing side effects or other complications. Trials are designed to answer specific research questions about a biomedical or behavioral intervention. For example, treatment trials might test experimental drugs or devices, new combinations of drugs, innovative approaches to surgery or radiation therapy, or behavioral interventions such as exercise training or medication adherence. Prevention trials test the effectiveness of approaches to prevent diseases or other adverse health conditions or to keep them from recurring. Comparative effectiveness research entails real-world comparisons of known interventions. (Also see the section on Chronic Diseases and Organ Systems in Chapter 2.) Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve people’s comfort and ability to continue the activities of daily life even as...
they deal with chronic illnesses or approach the end of life.

NIH also funds the development of consortia, cooperative study groups, and networks that enable a single institution or researcher to combine resources and knowledge with others. Consortia are particularly useful for studying rare diseases, and they allow clinical trials to more rapidly recruit sufficient numbers of participants to speed the delivery of new treatments to patients. The matrix of research support arising from such partnerships creates a whole that is much greater than the sum of the separate programs.

4. A key goal of NIH research efforts is to bring effective prevention and treatment strategies more quickly into practice to improve population health, both domestically and globally. The late (or postclinical) translational stage takes results from studies in humans and applies them to research on enhancing the adoption of best practices in the community. NIH investigates strategies for disseminating information to providers and the public about the latest research findings and encourages health care providers to participate in clinical research.

NIH collaborative activities in translational research take place within most ICs and almost every other HHS agency. The collaborations include working groups and committees such as the Biomedical Imaging in Oncology Forum, the Joint Working Group on Telehealth, and the Health Literacy Workgroup; a wide range of translational research such as projects on vaccine safety, child abuse and neglect, diabetes prevention, and health disparities; and database development and management such as the Stem Cell Therapeutics Outcomes Database.

The Federal government plays a critical role in focusing on gaps in clinical and translational research that would otherwise remain unaddressed by other entities (e.g., pharmaceutical companies, nonprofit organizations). Specifically, NIH supports clinical and translational studies unlikely to garner substantial investment by other sources because of insufficient financial incentives—for example, studies that address rare diseases, are considered high risk, or are based on lifestyle alterations or behavioral changes rather than drugs or devices.

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5. Important new discoveries can improve population health and reduce disease burdens only if they are integrated into care. Therefore, NIH is taking a lead in applying evidence-based methods to inform the public and health care practitioners about research results and facilitate the implementation of safe and effective interventions in the community and the clinic.

6. Although sometimes referred to as bench-to-bedside research, translational research is really a two-way street, with each stage informing and influencing the others. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often feed back to stimulate new basic investigations. Research on new outreach approaches and the comparative effectiveness of prevention and treatment strategies also are important activities to ensure the feasibility of such strategies and to inform the development of future interventions.

Every NIH component supports clinical and translational research. NIH’s ICs oversee a broad portfolio of clinical and translational research that encompasses intramural and extramural programs. (Also see the section on Extramural and Intramural Research Programs in Chapter 1.) NIH intramural research
laboratories are conducting cutting-edge biomedical research in a wide range of fields at its main campus in Bethesda, Maryland, and several satellite locations. Central to the intramural program is the NIH Clinical Center, the Nation’s largest hospital devoted entirely to clinical research. The Clinical Center serves more than 7,000 inpatients and more than 100,000 outpatients annually. To receive medical care at the Clinical Center, individuals need to meet the eligibility criteria for and agree to participate in a research trial.

The NIH extramural program, in addition to supporting both investigator- and NIH-initiated clinical and translational research, builds collaborations among institutions, industry (e.g., pharmaceutical companies), and local communities; sets up innovative centers of clinical and translational research; undertakes animal and other preclinical studies; and develops new resources and tools for research. Training and career development initiatives help ensure that enough highly trained and diverse groups of basic, clinical, and translational scientists are available with appropriate research knowledge to carry out the country’s biomedical and behavioral research agendas. (Also see the section on Research Training and Career Development in Chapter 3.)

NIH Roadmap initiatives are helping to accelerate and strengthen movement along the research continuum by ensuring that basic discoveries are translated into interventions to improve health. These initiatives are supporting the development of research networks, outcome assessment tools, core services and resources, policy enhancement and harmonization, and a Clinical and Translational Science Award (CTSA) program. Thanks to such programs, the clinical research enterprise is being transformed to speed the progression of new discoveries from bench to bedside and community.

Catalogs of Clinical and Translational Research Activities

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a catalog of clinical trials, provided here is a live link to the service called ClinicalTrials.gov, a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial’s purpose, who may participate, locations, and phone numbers for more details.

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a breakdown of study populations by demographic variable, provided here is a link to NIH’s Biennial Report on its tracking efforts regarding study demographics: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research. (Please also see Appendix D, which provides an excerpt of that report.)

In response to the mandate under SEC. 403 (a)(4)(C)(vi) for a catalog of translational research activities with other agencies of the Public Health Service, included here is a live link to the Catalog of Trans-HHS Translational Research Activities FYs 2007 & 2008. This is an excerpt from another congressionally mandated report, the Annual Report to the Secretary, HHS, on NIH Collaboration with Other HHS Agencies.

Summary of NIH Activities

NIH nurtures strategies that bring basic research discoveries to human studies, optimize the conduct of clinical research, and facilitate the transfer of new knowledge gained through research into clinical practice, thereby aligning and reinforcing the entire research continuum. The following summary delineates some specific strategies employed by the ICs to propel research along the research continuum and highlight a few examples from NIH’s robust portfolio of clinical and translational research.

Preclinical Research: Translating Basic Science Discoveries to Human Studies
Before investigators can conduct human studies, extensive basic and preclinical research must be done and a supportive infrastructure must be in place. NIH equips translational scientists with research tools, enhances opportunities for collaborative research, and provides resources for developing and testing new drugs before progressing to human studies. The result has been the creation of exciting possibilities in terms of new investigational drugs and devices ready for safety and efficacy testing in humans, including:

- In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions.
- Laboratories have been established to screen promising compounds for treating alcohol dependence in animal models, thereby enabling faster determination of those that merit advancement to large, multisite studies.
- NIH-supported investigations have successfully decoded the genome of the parasite that causes relapsing malaria and determined that the anti-malarial drug chloroquine may once again be used to prevent malaria in African children.

**Research Tools and Resources**

Preclinical research results derived from animal models are an essential element in the translational process of determining whether a basic science discovery is a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative will integrate data and information about animal models and make them available to health researchers to help them identify the most useful animal models for their research.

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Nonhuman primates are critical resources for translational research because of their close physiological similarities to humans. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. In FY 2008, more than 2,000 investigators used nonhuman primates from the NPRCs. One highlight of research conducted at a NPRC was the development and characterization of the first nonhuman primate model of a neurodegenerative condition—Huntington's disease. This new model will make it possible to study a wide range of therapeutic strategies to help people who have the devastating fatal disease.

Among the many research tools that NIH provides to promote early translational studies are biosample and data repositories. Central repositories allow additional studies on human tissue samples and data collected during clinical research, enhancing the value of each study and making optimal use of samples and data. The use of repositories also ensures that samples are stored under uniform conditions and are readily accessible to the scientific community. Samples and data are labeled with codes to keep the study participants’ information confidential. Although numerous regulations and policies apply to research on human samples and data, currently no comprehensive Federal policy covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens or data for research. To address this gap, NIH is developing draft guidelines for human specimen and data collections owned or supported by NIH. The guidelines cover ethical and regulatory issues and provide vital information about managing, accessing, sharing, and using the stored specimens and data. (Also see the section on Disease Registries, Databases, and Biomedical
A recent Alzheimer’s Disease Neuroimaging Initiative study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer’s disease and established a method and standard for testing for these biomarkers.

Researchers from several ICs are identifying, developing, and validating new biomarkers—physical, functional, or biochemical indicators of physiologic or disease processes. Biomarkers play important roles in the diagnosis of disease, identification of patient populations that could benefit from particular therapies, and the monitoring of treatment effectiveness. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a noteworthy example of an innovative public-private partnership for examining the utility of magnetic resonance imaging, positron emission tomography, or other methods to identify biomarkers that will enable clinicians and investigators to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer’s disease. ADNI has provided evidence to support development of a number of tools and methods now in use in the United States and abroad. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer’s disease and established a method and standard for testing for these biomarkers. (Also see the section on Neuroscience and Disorders of the Nervous System in Chapter 2 and the section on Alzheimer’s Disease Centers in Chapter 4.)


**Collaborative Science**

Oftentimes, translational research can be streamlined or conducted more economically when scientists within NIH, private industry, academia, private practices, or other institutions work in partnership to complement each other’s strengths and share costly resources or infrastructure. As its name implies, the NIH Bench-to-Bedside Program spans the research continuum with its focus on collaboration between basic and clinical investigators working to translate fundamental scientific discoveries into diagnostic and therapeutic applications at the bedside. This program also bridges the intramural and extramural research communities and fosters interagency collaborations.

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In addition, through the Strategic Partnering to Evaluate Cancer Signatures initiative, NIH is bringing together interdisciplinary teams at various institutions to discover, develop, and test biomarkers that can be used to characterize an individual’s disease or tumor. Armed with such information, clinicians can tailor a patient’s cancer treatment based on molecular characteristics of the patient and tumor. Several published studies have already demonstrated the usefulness of this personalized approach to cancer therapy. (Also see the section on Cancer in Chapter 2.)

**Resources for Developing and Testing Investigational Drugs**

NIH helps bridge the gap between drug discovery and clinical testing of promising new agents. Translating promising compounds into drugs for human use is a task that requires very specific,
interrelated activities. NIH provides state-of-the-science preclinical drug development resources. Specifically, NIH helps investigators by providing large quantities of promising investigational drugs to test in clinical trials, and clarifying regulatory issues so that FDA requirements are likely to be satisfied when the new investigational drugs are ready for testing in the clinic. For example, the NCI Experimental Therapeutics program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and follows a series of progressive steps leading to early-phase clinical studies. The NExT program aims to produce a diverse portfolio of assays and imaging tools that are available in the public domain. It is anticipated that this investment will reap many benefits by making a library of new molecular tools available to all researchers in the cancer research community for use in assessing new targeted drugs and diagnostics. (Also see the section on Cancer in Chapter 2.)

A menu of preclinical drug development contract resources is offered through one of NIH’s Roadmap initiatives, the Rapid Access to Intervention Development (RAID) program. The NIH-RAID program makes accessible, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn’s disease.

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To move basic research on Alzheimer’s disease and associated disorders into the realm of translational research and drug testing in clinical trials, NIH is providing resources for preclinical development of investigational drugs and toxicology studies for academic and small business investigators who lack the resources to perform the required evaluations of promising therapeutic compounds. Several compounds already are undergoing testing, including anti-hypertensive drugs, anti-inflammatory drugs, and novel small molecules. (Also see the section on Neuroscience and Disorders of the Nervous System in Chapter 2.)

Similarly, NIH has developed several focused translational research initiatives over the last decade in the area of neurological disorders. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for spinal muscular atrophy using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal of a human clinical trial beginning in 2010. (Also see the section on Neuroscience and Disorders of the Nervous System in Chapter 2.)

Clinical Research: Learning Which Interventions Work

Clinical research helps scientists develop and test interventions and new treatments. There are many types of clinical research. For example, some observational clinical research studies involve following a group of patients with a condition and determining their symptoms and responses to treatment in order to refine medical practice. Some studies help researchers and clinicians determine whether dosing schedules, behavioral changes, and other elements of a treatment plan are realistic and appropriate. Clinical research sometimes overlaps with the category of epidemiological studies, which is described earlier in this chapter. These studies can help researchers develop new interventions that can be evaluated later in clinical trials.

Generally, clinical trials, particularly those evaluating drugs or medical devices, are conducted in
phases, each of which helps scientists answer different questions. In a Phase I trial, researchers test an experimental drug or treatment in a small number of people (20-80) to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve larger numbers of people (100-300) and evaluate the safety and effectiveness of the study drug or treatment. In Phase III trials, the experimental study drug or treatment is given to large numbers of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase IV, or postmarketing, studies are conducted to gather information associated with long-term use in various populations.

The randomized clinical trial has long been considered the gold standard for evaluating the effectiveness of investigational treatments. "Randomization" means that subjects are assigned by chance to either the investigational intervention or the control group. The control group might include interventions such as usual care; best proven care, if known; no treatment; or placebo. The specific clinical trial design is dependent upon the research questions posed. In addition to the use of control groups, clinical trials often use "blinded" or "masked" study designs, in which patient participants are purposely not told whether they are in the intervention or the control group. If feasible, clinical trials are often "double-blinded" or "double-masked," meaning that neither researchers nor participants know which people receive the intervention to ensure that the study results are unbiased.

Participation in clinical trials gives people an opportunity to contribute to the research effort and potentially gain early access to experimental treatments that might prove effective. For some participants, a study can provide expert medical care at a leading health care facility. Research risks and potential benefits are carefully balanced, and the burdens and benefits of participating are shared equally by appropriately including both sexes and people of all races/ethnicities and ages (see Appendix D). Balanced inclusion in trials allows investigators to know whether an intervention works equally well in different populations. NIH supports outreach efforts to recruit and retain children, women, and minorities in clinical studies. In addition, NIH recognizes the importance of developing sound scientific bases for pediatric care while protecting children adequately in research settings. NIH policy, therefore, requires that children (i.e., individuals younger than 21 years of age) be included in human subjects research conducted or supported by NIH, unless there are sound scientific or ethical reasons for excluding them. To help people access information about clinical trials for which they may be eligible, the ClinicalTrials.gov website offers general information about clinical trials and provides a searchable database of specific studies around the world.54

NIH recognizes that the involvement of human beings as participants in research creates ethical and regulatory responsibilities for the investigators and institutions conducting such research. NIH clinical research encompasses the principles of respect for persons, beneficence, and justice. Most clinical research is federally regulated with built-in safeguards to protect the participants. NIH, therefore, has established a system of research, review, approval, and oversight to assist investigators in understanding ethical principles and complying with regulatory requirements to maximize safety for research subjects. The informed consent process is carefully designed to ensure that study participants understand the risks and possible benefits of the research. Various NIH initiatives and programs seek to harmonize regulatory aspects governing the conduct of clinical research to ensure that studies are conducted with scientific rigor, with minimal burdens on research subjects and investigators, and with utmost consideration for the safety, rights, and welfare of subjects. (See also Ensuring Responsible Research in Chapter 1.)

54 As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in www.clinicaltrials.gov.
NIH support and activities along the research continuum are enriching the pipeline of biomedical discoveries. NIH funnels the majority of its funding for clinical trials to its extramural partners, which operate at the regional, State, and local levels. Studies often are conducted at multiple institutions. Such multisite clinical trials help investigators quickly recruit enough subjects for studies; give the public the widest possible access to clinical studies; and address the special health concerns of high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. To test investigational therapeutic and preventive strategies in the most expeditious way and hasten their entry into the clinic, NIH is supporting a wide variety of collaborations, research centers, and networks to conduct efficient multicenter clinical trials.

To investigate effective treatments for mental disorders, NIH uses its extensive clinical trials networks as platforms for research. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Depression Trials Network, for example, is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different depression medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term.

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NIH equips networks of investigators with the tools they need for successful collaboration and information sharing. NIH supports many clinical research networks by funding ongoing infrastructure that provides means of standardizing data reporting to enable seamless data and sample sharing across studies. Through NIH-funded informatics and other technologies, researchers are better able to broaden the scope of their research and avoid duplicating research efforts, thereby freeing time and funds to address additional research questions.

Among the numerous networks established by NIH that have generated significant findings are the Maternal and Fetal Medicine Units Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Collaborative Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, the Alzheimer’s Disease Cooperative Study, and the Global Network for Women’s and Children’s Health Research. Additionally, the NCI Community Cancer Centers Program is encouraging more patient and physician involvement in NIH-sponsored cancer trials, establishing new methods for tracking minority accrual, and improving specimen collection. NIH recently has initiated several additional networks, including the notable examples of the Hepatitis B Clinical Research Network and the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network. These new networks are expected to generate significant findings in the future.

Addressing Gaps in Research

In terms of clinical evaluation of drugs, there is no clear line where NIH-supported work stops and the pharmaceutical industry picks up. Every drug candidate presents its own profile of benefit and potential for gains in public health as well as financial risk. NIH’s aim is to be sure that all important leads are
followed until they are mature enough to attract private-sector interest or until they reach a dead end. About half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed by NIH. Cisplatin for treating testicular, ovarian, and lung cancer; paclitaxel (Taxol) for treating several different cancers; and fludarabine phosphate for treating lymphoma are examples of how NIH involvement in early-stage drug development led to products that were licensed to commercial organizations and reached the market. In addition, NIH involvement has been central in developing effective interventions for diagnosis, management, or monitoring of HIV/AIDS, tuberculosis, arthritis, malaria, and many other conditions.

Government-funded research is particularly vital for the study of rare diseases. Not only do affected individuals benefit from new treatments that industry does not have the incentive to bring to market, but insights gained from such research often provide knowledge relevant to understanding more common diseases. For these reasons, NIH-funded investigators are studying an inherited retinal degenerative disease called Leber's congenital amaurosis (LCA), which causes severe vision loss in infancy or early childhood. NIH intramural scientists discovered that the \( RPE65 \) gene plays a key role in the visual cycle—the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in this gene disrupt the visual cycle, resulting in LCA and blindness. As described in reports published in 2008 and 2009, an NIH-supported Phase I clinical trial of \( RPE65 \) gene transfer in LCA found the treatment is safe and that visual function improved. Additional studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. This clinical research is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a therapy for eye disease.

Because behavioral interventions generally do not involve marketable products or services, NIH has a special role to play in research on how changes in behavior can improve health. For example, the Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Participants in the ILI group achieved clinically significant weight loss in the first year of the study; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in health-related quality of life and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose levels, as compared to a control group receiving standard diabetes support and education. Look AHEAD seeks to determine whether the ILI reduces the incidence of heart attack and stroke, the leading causes of death among people with type 2 diabetes. This multicenter, randomized clinical trial involves several ICs as well as the Centers for Disease Control and Prevention.

The Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss in overweight or obese people with type 2 diabetes through decreased caloric intake and increased physical activity.

One area where human research data often are lacking is the study of environmental effects on human health. Scientists working at the new Clinical Research Unit located on the NIH campus in Research Triangle Park, North Carolina, aim to narrow the gap between research and health care. The mission of the Clinical Research Unit is to translate basic laboratory findings to human studies; investigate interactions between genetic susceptibility and environmental factors in complex human traits and diseases; identify populations at risk; and develop novel preventive and therapeutic strategies to combat human diseases. Scientists who use the new facility are embarking on a diverse array of research studies involving pulmonary diseases, medical genetics, cardiovascular diseases, and reproductive health. The Clinical Research Unit also will provide advanced training opportunities for students and postdoctoral fellows whose research interests require access to clinical samples and
Bariatric surgery is sometimes used in clinical practice as a treatment for severely obese adolescents despite a lack of evidence demonstrating its benefits for this population. NIH is addressing this research gap by supporting an observational study of teens already scheduled for surgery, Teen-LABS (Longitudinal Assessment of Bariatric Surgery). The Teen-LABS study is built upon the framework of the LABS consortium a group of surgeons, physicians, and scientists studying adult bariatric surgical outcomes. The Teen-LABS study will help determine whether bariatric surgery is an appropriate treatment option for extremely obese adolescents.

In response to another knowledge gap, NIH has launched the Clarification of Optimal Anticoagulation through Genetics (COAG) trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin, the most commonly used oral anticoagulant in the United States. This prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning treatment with warfarin. The COAG study will help determine whether knowledge of some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The drug is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes, but the ideal dosage varies widely from one person to another. Getting the wrong amount of warfarin can be dangerous: If the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The knowledge gained in COAG will make significant scientific contributions to several medical specialties and help advance the field of personalized medicine.

Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in biodefense measures. Biological weapons in the possession of hostile states or terrorists, as well as naturally occurring emerging and reemerging infectious diseases, are among the greatest security challenges to the United States. NIH, therefore, is fostering unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against such biological threats as smallpox; botulism; Ebola, Marburg, and West Nile virus; avian influenza; and plague. (Also see the section on Infectious Diseases and Biodefense in Chapter 2.)

**Putting Clinical Research Results into Practice**

Throughout this report are descriptions of important studies that are changing the way health care is practiced in this country, improving public health and enhancing well-being. To fully realize the potential of new interventions, research results must be disseminated and put into widespread use. NIH carries out comparative effectiveness research (CER), investigates strategies for adoption of new evidence at the community level, trains health care providers in research skills, disseminates information to providers and the public based on the latest research findings, and sponsors research to learn about the most effective ways to disseminate such findings.

*Comparing the Effectiveness of Different Therapies or Strategies*

CER is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real-world settings. The purpose of such research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and sub-groups. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies. This research necessitates the development, expansion, and use of a
variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.\textsuperscript{55}

In efficacy research, such as a drug trial for FDA approval, the question typically is whether the treatment is efficacious under ideal, rather than real-world, settings. The results of such studies, therefore, are not necessarily generalizable to all patients or situations. CER is intended to complement this approach by helping patients and clinicians make decisions about which treatment is the best choice in given situations. CER also is called patient-centered health research or patient-centered outcomes research to illustrate its focus on patient needs.\textsuperscript{56}

NIH has a long history of supporting landmark CER studies that challenge existing standards of clinical practice. NIH was awarded $400 million from the American Recovery and Reinvestment Act of 2009 (ARRA) for CER. A CER Coordinating Committee has been initiated to ensure optimal use of the recovery funds, make funding recommendations to the NIH Director, and develop a long-term CER research plan.

NIH investments are generating CER findings of public health significance, high relevance to clinical medicine, and scientific excellence. For example, the Spine Patient Outcomes Research Trial (SPORT) has helped answer questions about how best to treat various types of chronic low-back pain. Before SPORT, patients and physicians lacked data that compared treatment outcomes that could be used to guide people who were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, and others feared that delaying surgery might cause even more damage. SPORT has demonstrated that, indeed, surgery is superior to nonoperative treatments for the most common causes of chronic, severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). In addition, the study revealed that people who have one of these conditions are not subjecting themselves to further harm if they adopt a wait-and-see approach before committing to surgery.

\textit{The Spine Patient Outcomes Research Trial (SPORT) has helped answer questions about how best to treat various types of chronic low-back pain. This is an example of NIH’s commitment to comparative effectiveness research.}

CER studies are ideal for providing physicians with evidence-based guidance to help them identify the safest and most effective therapies for their patients. For example, the NIH-supported Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial simultaneously compared two cardiovascular treatment approaches and two diabetes control strategies to improve survival and to lower the risk of heart attacks and strokes. The study, published in 2009, demonstrated that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of cardiovascular disease (CVD) event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.


**Changing Clinical Practice**

It is not enough merely to have the infrastructure needed to address the ambitious goal of implementing science-based interventions and practices in community settings. Strategies to encourage adoption of proven approaches and treatments also are needed, as well as ways to tailor such approaches to specific populations or even to individuals. For example, NIH has made significant advances in elucidating the scientific bases for the effects of several treatment approaches based on complementary and alternative medicine (CAM). However, results of a national survey designed to gauge the potential for CAM research to influence clinical practice revealed a need for more effective dissemination of research findings. Acupuncturists, naturopaths, internists, and rheumatologists were asked about their awareness of two major NIH-sponsored studies of acupuncture or glucosamine/chondroitin for treating osteoarthritis of the knee. According to the survey results published in 2009, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both. Although CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice, the survey points to the need to train all clinicians in interpretation and use of evidence from research studies and to improve the dissemination of research results.

**NIH has made significant advances in elucidating the scientific bases for the effects of several treatment approaches based on complementary and alternative medicine.**

In addition, NIH supports 13 Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging to improve the health, quality of life, and productivity of middle-aged and older people. The centers work to facilitate translation of basic behavioral and social science to practical outcomes by developing new technologies and by stimulating new use-inspired research (that is, research focused on meeting a societal need, usually for a device to improve quality of life for certain populations). Roybal investigators have made several key discoveries. One center, for example, has developed tools and technologies for identifying older adults at risk for automobile crash involvement and is working with industry partners to develop and disseminate products based on these tools. Another center has developed an electronic in-home assessment tool to facilitate early detection of changes in health or memory. Companies have used this model to develop related products, and the model has spurred several new NIH-funded research projects, including the development of a new medication tracker for older adults.

The Pharmacogenetics Research Network (PGRN) is ushering in the era of personalized medicine. The goal of pharmacogenetics research is to enable doctors to move beyond the current, one-size-fits-all approach to treatment and toward prescribing the drugs and dosages that will work best for each person. NIH established the PGRN to study how genes affect the way a person responds to medicines. The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the PGRN, sponsors data-sharing consortia. The International Tamoxifen Pharmacogenetics Consortium is gathering genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects. The International Severe Irinotecan Neutropenia Consortium is assembling a large data set to definitively answer questions relating to genetic effects on adverse outcomes of irinotecan anticancer therapy and to provide tools for evaluating toxicity risk.

**Disseminating Research Findings**

NIH produces the PubMed/MEDLINE database, the world’s most heavily used source of information about research findings published in journal articles. (Also see the section on Disease Registries, Databases, and Biomedical Information Systems in Chapter 3.) NIH also is taking the lead in special efforts to inform the public and health care practitioners about research results that have the potential to improve health (also see the section on Health Communication and Information Campaigns and...
Clearinghouses in Chapter 3). The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP disseminates the results of the DPP by encouraging people to take small steps to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in an educational campaign, "Control Your Diabetes. For Life." The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups that are disproportionately burdened by kidney disease, type 2 diabetes, and obesity.

In keeping with the NIH Public Access Policy (also see the sections on Disease Registries, Databases, and Biomedical Information Systems in Chapter 3), scientists are required to submit final, peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central. This practice ensures that the public has access to the published results of NIH-funded research to help advance science and improve human health.

Located in the NIH Office of the Director, the Office of Medical Applications of Research (OMAR) works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. To date, NIH has conducted more than 120 consensus development conferences and 30 state-of-the-science conferences. Consensus and state-of-the-science statements are disseminated widely after the conference either to modify clinical practice when evidence strongly supports the use (or avoidance) of a particular intervention or to direct future research when important gaps in knowledge have been identified. The consensus statements that result from these conferences are shared widely with health care providers, policymakers, patients, and the media. In 2008, consensus statements were issued on hydroxyurea treatment for sickle cell disease and on the management of hepatitis B. In 2009, state-of-the-science statements were released on the use of family histories in the primary care setting and on the diagnosis and management of ductal carcinoma in situ.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish evidence-based clinical practice guidelines that describe a range of generally accepted approaches for the diagnosis, management, or prevention of specific diseases or conditions. In addition, NIH clinical guidelines provide recommendations that patients and their doctors can use to develop individual treatment plans tailored to the specific needs and circumstances of the patient. In 2009, two new guidelines for the prevention and treatment of HIV-associated co-infections were issued: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents and Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. The Pediatric Cardiovascular Risk Reduction Initiative guideline is slated for release in mid 2010.

Bolstering the Research Continuum

NIH is committed to restructuring the clinical research enterprise, a key objective of the NIH Roadmap for Medical Research, which comprises a series of initiatives funded by the NIH Common Fund. These
high-impact initiatives are designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone, but which the agency as a whole can address to make the biggest impact possible on the progress of medical research. To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives will work toward improving the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field.

Building Capacity for Clinical and Translational Research

Drawing on the momentum of the NIH Roadmap and extensive community input, the Clinical and Translational Science Award (CTSA) program is creating academic homes for the discipline of clinical and translational science at institutions across the country. As of fall 2009, this network of research institutions consists of 46 awardees in 26 states. The consortium will eventually link about 60 institutions around the Nation. The program encourages the development of novel methods and approaches to clinical and translational research, enhances informatics and technology resources, and improves training and mentoring to ensure that new investigators can navigate an increasingly complex research system. CTSA s are enabling researchers to work in unprecedented ways to advance medical research across many disease areas and conditions, including cancer, neurological diseases, cardiovascular disease, diabetes, and obesity.

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A key ingredient in research success is the translation of laboratory bench insights to the patient bedside and back again, to inspire new laboratory investigations that ultimately improve patient care and public health. In this vein, the Centers of Research Translation (CORT) program was launched to unite basic and clinical research. Each CORT encompasses at least three projects, including one clinical and one basic research study. The three most recently funded CORTs are the Center for Genetic Dissection of SLE (lupus), the Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints, and the Center for Psoriasis Research Translation.

Researchers are increasingly conducting studies in community clinics, doctors' offices, and other health care facilities as innovative means of building capacity across the Nation and ensuring that diverse populations are involved in research. For example, NIH fosters scientifically rigorous research in oral health care in three dental practice-based research networks (PBRNs) to address the longstanding lack of high-quality research data to guide everyday treatment decisions in the dentist’s office. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. Over the course of the grant period, the networks will each complete approximately 15 to 20 short studies, several of which have already been reported in the scientific literature.

Developing the Research Teams of the Future

Through its career development initiatives, NIH is preparing to meet the need for a multidisciplinary, well-trained cadre of researchers at every point in the research continuum. (Also see the section on Research Training and Career Development in Chapter 3.) For example, a key component of the CTSA program is the creation of graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next
generation of clinical and translational researchers.

In addition, NIH develops, administers, and evaluates clinical research training initiatives that contribute to the professional growth of the clinical and translational research community, including medical and dental students, physicians in residency and in fellowship programs, established investigators, allied health professionals, and community partners. A clinical research curriculum is offered at NIH and other domestic and international locations. Extramural researchers have a new opportunity to access rich training experiences via a "Clinical Research Management Sabbatical," designed to help them develop leadership skills for conducting clinical research. Partnerships between NIH and extramural collaborators and industry have contributed to the menu of educational offerings. For example, via videoconferencing, Duke University School of Medicine offers NIH physicians and dentists an opportunity to receive a master's degree of health sciences in clinical research. The intramural Clinical Research Training Program, a partnership supported by NIH and a grant to the Foundation for the NIH from Pfizer, Inc., trains 30 advanced medical and dental students annually in clinical or translational research.

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The Research Centers in Minority Institutions (RCMI) program develops and enhances the research infrastructure of minority institutions by expanding human and physical resources for conducting basic, clinical, and translational research. The program, which began in 1985 in response to congressional report language (see the description of the RCMI program in the notable examples that follow under the theme "Bolstering the Research Continuum"), provides grants to institutions that award doctoral degrees in the health professions or health-related sciences and have enrollments that are predominantly students from minority communities underrepresented in the biomedical sciences. The RCMI Translational Research Network (RTRN) is a national consortium of clinical and translational researchers in the RCMI Centers, working in collaboration with investigators from other academic health centers, community health providers, and the public to focus their collective efforts on addressing health disparities. RTRN researchers focus on diseases that disproportionately affect minority and other medically underserved populations. The multisite collaborative research supported by RTRN infrastructure, training, and resources is ensuring that discoveries generated in the laboratory are being translated into clinical studies. (Also see the section on Minority Health and Health Disparities in Chapter 2.)

The RCMI Clinical Research Education and Career Development (CRECD) Awards provide didactic training and mentored clinical research experiences to develop independent researchers who can lead clinical research studies, especially those addressing health disparities. RCMI CRECD awards help develop and implement degree programs in minority institutions that train doctoral and postdoctoral candidates in clinical research.

Improving Research Efficiency

Maximizing human subject protection, while facilitating translational and applied clinical research, has become a critical challenge in the 21st century. To increase the efficiency and effectiveness of the clinical research enterprise, NIH is examining barriers to clinical research and striving to harmonize regulations and policies that pertain to its conduct and oversight.
The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research.

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research. As the lead Federal agency supporting clinical research, it is incumbent upon NIH to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight. The CRpac program works on an array of issues and activities usually in close collaboration with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research. NIH also is partnering with several other Federal agencies to ensure that a standard reporting format is available for investigators to report adverse events associated with their clinical research. The development of the Basal Adverse Event Report (BAER) will allow investigators to satisfy the different safety reporting requirements for all Federal agencies. NIH also has specific initiatives to restructure the clinical trials enterprise in the area of oncology. For example, the Standard Terms of Agreement for Research Trials are designed to help cut the time spent on contract negotiations between pharmaceutical/biotechnology companies and academic medical centers. In addition, the Clinical Trials Reporting Program is establishing a comprehensive database containing regularly updated information on all NCI-funded interventional clinical trials. Grantees are requested to enter specific information about each clinical trial into the database. This information will be used to coordinate research efforts to optimize the Nation’s investment in cancer research.

Conclusion

The results of NIH’s commitment to clinical and translational science are apparent in the following highlights describing some of the important accomplishments and ongoing initiatives in these rapidly developing areas of research.

Notable Examples of NIH Activity

**Key**

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<td>GPRA Goal</td>
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IC acronyms in **bold** face indicate lead IC(s).

Preclinical Research: Translating Basic Science Discoveries to Human Studies

**New Therapeutic Strategy for Retinitis Pigmentosa:** Retinitis pigmentosa (RP) is a set of genetic diseases that cause the death of rod photoreceptors, the light-sensitive cells in the peripheral retina that help us see in dark and dimly lit environments. Unfortunately, the death of rod cells causes the death and degeneration of healthy cone cells. Cone photoreceptors provide sharp visual acuity, allowing us to read, recognize faces, drive a car, or perform other daily tasks that require hand-eye coordination. If cone cells could be preserved, patients with RP could avoid severe impairment. Mounting evidence suggests that cone cells die due to oxidative damage because the blood vessels in
the retina cannot regulate blood flow to reflect decreased oxygen demand after rod cell death. NIH-supported investigators recently began efforts to bolster innate production of antioxidants by overexpressing genes that defend against oxidative assault. In a novel set of experiments, investigators developed a mouse strain with RP that also overexpressed various genes involved in the antioxidant defense system. Overexpression of superoxide dismutase 2 (SOD2) and catalase, two powerful antioxidant enzymes, preserved cone cells. These findings support the concept of a gene-based treatment strategy to strengthen the body's antioxidant defense system in patients with RP.

- For more information, see [http://www.nature.com/mt/journal/v17/n5/abs/mt200947a.html](http://www.nature.com/mt/journal/v17/n5/abs/mt200947a.html)
- (E) (NEI)

**Translational Research on Alzheimer's Disease (AD):** To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NIA) (GPRA)

**Lupus:** There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.


Pediatric Rheumatic Diseases: A rare, genetically inherited, inflammatory condition recently was discovered by researchers from NIH and other institutions. DIRA ("deficiency of the interleukin-1 receptor antagonist") patients often are misdiagnosed and do not receive appropriate treatment because their disease is characterized by symptoms seen in many illnesses: recurring episodes of systemic inflammation in multiple tissues, such as skin, bones, and joints. Inflammation is crucial in fighting infections, but uncontrolled, chronic inflammation can cause organ and tissue damage. It was found that DIRA symptoms are caused by a defective gene for a protein (IL-1Ra) that normally inhibits molecular signals for inflammation. Understanding DIRA symptoms and pathogenesis can guide better treatment for the disease, and may help clarify the IL-1Ra gene's role in promoting inflammation in more common diseases. On another front, children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, which is a potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease. Statins also have intrinsic anti-inflammatory properties. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial has been testing whether statins can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus. Another prospective study of adult and pediatric lupus patients confirmed previous observations, that children have more active disease than adults at the time of diagnosis. Over
time, pediatric lupus patients also have more aggressive and severe disease than adult lupus patients.

- For more information, see [http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp)
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E/I) (NIAMS)

**New Indications for Established Agents to Treat Chronic Disease:** When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (I) (NIA)

**NIH Countermeasures Against Chemical Threats (CounterACT) Research Program:** The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The Network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

- For more information, see [http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm](http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm)
Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 3: Molecular Biology and Basic Research

(E) (NINDS, NIDA, NIAID, NICHD, NIEHS, NIGMS) (GPRA)
Translational Research with Gene Transfer for X-Linked Juvenile Retinoschisis (XLRS), a Congenital Eye Disease of Boys: XLRS is a rare but severe developmental abnormality of the retina found in children that causes impaired visual acuity and retinal detachment. Clinical examination shows small cysts within the macula, the center of the retina, and a splitting (or schisis) of the layers of the peripheral retina. XLRS is caused by a mutation in a single gene, retinoschisin, which is thought to play a structural role in the retina. NIH intramural investigators are developing gene transfer therapy to ameliorate and possibly cure XLRS. In other gene transfer clinical trials for Leber congenital amaurosis, a single subretinal injection of the gene-carrying vector reached about 25 percent of the retina. However, subretinal injection is unsuitable for XLRS as the retina is too fragile and the entire retina needs treatment to prevent further schisis. To this end, NIH intramural investigators injected a vector containing copies of the retinoschisin gene into the vitreous, the clear, jelly-like fluid inside the eye, using a mouse model of XLRS. This allowed retinoschisin to penetrate the entire retina in amounts similar to healthy retinas. Treated mice demonstrated a decrease in schisis and showed improved retinal activity 11-15 weeks after treatment. This study offers evidence that injection into the vitreous is a viable method to deliver gene therapy to the neural retina.

- For more information, see [http://www.nature.com/gt/journal/v16/n7/full/gt200961a.html](http://www.nature.com/gt/journal/v16/n7/full/gt200961a.html)
- (I) (NEI, NIDCD)

The NIH Rapid Access to Intervention Development (RAID) Program: The NIH-RAID program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn's disease. The NIH-RAID program is part of the NIH Roadmap for Medical Research.

- For more information, see [http://nihroadmap.nih.gov/raid/index.aspx](http://nihroadmap.nih.gov/raid/index.aspx)
- (E) (NINDS, Common Fund - all ICs participate)

Translational Research for Neurological Disorders: The Anticonvulsant Screening Program has catalyzed the development of six epilepsy drugs now on the market; the Neural Prosthesis Program has pioneered devices to restore lost nervous system functions; the Intramural Program has developed the first enzyme therapy for inherited disorders; and investigator-initiated research programs have led to development of FDA-approved drugs by industry. In 2003, NIH launched a program designed to expedite preclinical therapy development across all neurological disorders. The Cooperative Program in Translational Research supports academic and small business investigator-initiated projects in single laboratories or consortia, using milestone-driven funding and peer review tailored to the requirements of therapy development. Projects are developing drug, stem cell, or gene therapies for amyotrophic lateral sclerosis (ALS), Batten disease, epilepsy, Huntington's disease, muscular dystrophies, Parkinson’s disease, tuberous sclerosis, and stroke, among other disorders. NIH also has developed several focused translational research initiatives over the last decade. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for SMA using a “virtual pharma” strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal to begin human clinical trials as soon as
possible. Translational research is a "signature project" for NINDS investment of American Recovery and Reinvestment Act funds.

- For more information, see [http://www.ninds.nih.gov/funding/research/translational/index.htm](http://www.ninds.nih.gov/funding/research/translational/index.htm).
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS) (ARRA)

**Confronting the Challenge of Antimicrobial Resistance:** Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

- For more information, see [http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm](http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm).
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: Genomics.
- (E/I) (NIAID) (GPRA)

**Development and Testing of Malaria Vaccines and Therapeutics:** NIH supports recent calls to work toward the goal of malaria eradication. Means toward this end include stopping the spread of the malaria parasite, reducing the burden of disease region by region, and eliminating the parasite from malaria-endemic countries and then from every country throughout the world. In FY 2008, NIH assessed its malaria research portfolio and identified opportunities for the next phase of malaria research. This led to the publication of the Strategic Plan for Malaria Research and the related NIAID Research Agenda for Malaria. NIH recently launched a new initiative, the International Centers of Excellence in Malaria Research, to support a novel, global, multidisciplinary approach to understanding malaria in the evolving context of control, elimination, and eradication. NIH researchers recently began clinical investigations to assess malaria biology and pathogenesis with collaborators in Mali and Cambodia, activities that resulted in the completion (or expansion) of research facilities and hospitals to support new malaria research programs. Examples of NIH-supported advances in malaria research include:

- Successfully decoding the genome of the parasite that causes relapsing malaria and determining that the anti-malarial drug, chloroquine, may once again be used to prevent malaria in African children.
- Investigating novel vaccine strategies, such as those that block transmission of the malaria parasite to the mosquito vector, and exploring the molecular biology of the parasite and its interaction with
Ten vaccine candidates currently are in preclinical development and five are in clinical trials.

- For more information, see [http://www3.niaid.nih.gov/topics/Malaria/](http://www3.niaid.nih.gov/topics/Malaria/)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* (E/I) (NIAID)

**Medical Countermeasures Against Nuclear and Radiological Threats:** NIH continues to lead the HHS effort to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical countermeasures are in the early stages of discovery; however, substantial effort focuses on later development as lead compounds are identified. Animal model testing is underway for 59 medical countermeasures for hematopoietic (HE) acute radiation syndrome (ARS), 18 for gastrointestinal (GI) ARS, 13 for radiation-induced lung pneumonitis and/or fibrosis, 13 for kidney injury, 7 for brain injury, and 17 for skin, including combined injuries (radiation plus burns or wounds). Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA), which may be used to treat victims with internal radionuclide contamination from fallout or “dirty bombs,” are in development. Research into 6 lead, orally bioavailable compounds with enhanced properties for removing radioactive isotopes from the body also is ongoing. Interactions with 87 biotechnology companies through an advanced development contract have led to the identification and initial animal efficacy confirmation for 7 HE-ARS candidate medical countermeasures and 2 GI-ARS candidate medical countermeasures. Other areas of research include characterization of genomic, proteomic, metabolomic and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.

- For more information, see [http://www3.niaid.nih.gov/topics/radnuc/](http://www3.niaid.nih.gov/topics/radnuc/)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* (E) (NIAID) (ARRA)

**Rapid Research Response to Emerging Disease Threats:** The sudden and unpredictable emergence of infectious diseases requires advance preparation to safeguard public health. Because the groundwork of basic research can be crucial when new health threats arise, NIH conducts and supports research to increase basic knowledge of infectious diseases, and advance development of effective diagnostics, therapeutics, and vaccines. In the case of severe acute respiratory syndrome (SARS), for instance, NIH's broad portfolio of basic research grants on coronaviruses was critical to understanding the new pathogen. NIH has developed new funding initiatives for accelerated, targeted research to encourage collaborative and product development-oriented projects. NIH also provides needed infrastructure and resources to support the research community in the event of a public health emergency. For example, the national network of Vaccine and Treatment Evaluation Units provides a ready means to conduct clinical trials to evaluate vaccines and treatments for outbreaks such as the novel 2009 H1N1 influenza. In 2009, NIH awarded new funding for 1 and renewed funding for 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). The RCEs are a critical component of the U.S. research infrastructure for infectious diseases, and are designed to respond flexibly to changing scientific needs and priorities. RCE researchers are developing new or improved ways to treat, diagnose, or prevent illnesses, including anthrax, West Nile fever, plague, and dengue fever. The RCEs are prepared to provide scientific expertise to first responders in an infectious disease-related emergency, whether such an emergency arises naturally or
through an act of bioterrorism.

- For more information, see [http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm](http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm)
- This example also appears in Chapter 2: Infectious Diseases and Biodefense
- (E) (NIAID) (ARRA)

**Renewed Focus on Basic HIV Vaccine Discovery Research:** In March 2008, NIH sponsored a Summit on HIV Vaccine Research and Development. Participants reached consensus that NIH should increase its emphasis on basic vaccine discovery research. Toward this end, the Highly Innovative Tactics to Interrupt Transmission of HIV program was established to stimulate research on novel, unconventional, "outside the box," high-risk, high-potential, and high-impact approaches that might provide long-term protection from HIV acquisition. The Basic HIV Discovery Research initiative also was initiated to support generation of knowledge that will inform new conceptual approaches to HIV vaccine design. NIH also funds new research through the B Cell Immunology for Protective HIV-1 Vaccine program to foster fundamental research on B cell immunology to derive new understanding and approaches for development of HIV vaccines. NIH continues to conduct clinical research as appropriate and seeks to answer basic research questions through clinical trials. NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV. It is hoped that this study will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccine candidates.

- For more information, see [http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/](http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/)
- This example also appears in Chapter 2: Infectious Diseases and Biodefense
- (E) (NIAID) (GPRA)

**Tackling Neglected Tropical Diseases:** Neglected tropical diseases (NTDs) such as lymphatic filariasis, schistosomiasis, leishmaniasis, and dengue take a tremendous toll on global health. The World Health Organization estimates that more than 1 billion people—approximately one-sixth of the world's population—suffer from at least 1 NTD. NIH scientists and NIH-supported researchers in countries where NTDs are widespread are developing vaccines and treatments for diseases such as leishmaniasis and identifying new drugs for sleeping sickness and Chagas' disease. NIH-supported researchers also have made a significant leap forward in the battle against schistosomiasis by identifying potential new therapies through the use of genomics and medicinal chemistry. The Vector Biology Research Program supports research on several vectors that transmit agents of NTDs. Through this program, a project in French Polynesia aims to reduce populations of *Aedes polynesiensis*, a mosquito species responsible for spreading filariasis. Other investigators studying the mosquito immune response against filarial worms hope to identify targets for blocking development of the worm inside the mosquito. NIH scientists studying the salivary proteome of NTD vectors are identifying novel biologically active compounds and vaccine targets. In FY 2009, NIH-supported researchers reported the first complete genome sequences for two parasite species that cause schistosomiasis. Finally, a public-private partnerships for product development program is designed to accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for infectious diseases of global importance for which commercial markets currently provide insufficient
incentive for corporate investment.

- For more information, see [http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm](http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* (E/I) (NIAID)

### Three-Pronged Approach to Fighting HIV:

The unique and formidable challenge of combating HIV is spurring leaders in medicine and public health to consider a bold new approach to fighting it. NIH and other organizations are exploring a three-pronged approach to fight the HIV/AIDS pandemic. The first prong is pre-exposure prophylaxis (PrEP), which uses antiretroviral therapies to prevent HIV infection among people who are not infected with HIV but who are at high risk of becoming infected. NIH currently is testing this approach in clinical trials such as the iPREX study, which is examining whether the HIV treatment Truvada can prevent HIV infection among HIV-negative men who have sex with men. The second prong is a novel approach, based on mathematical modeling, which suggests that the implementation of a universal HIV testing program and the immediate initiation of antiretroviral therapy (ART) for those individuals who test positive could dramatically reduce the number of new HIV cases within the decade. NIH now is addressing a number of critical scientific issues to determine the feasibility of this approach. Finally, NIH is strongly encouraging research to cure HIV by eliminating HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ART who have an undetectable viral load. Stopping ART treatment results in a rebound of viral load to levels seen prior to treatment. NIH has launched a new initiative to identify these reservoirs and develop techniques to eradicate them.

- Dieffenbach CW, Fauci AS. *JAMA* 2009;301(22):2380-2. PMID: 19509386.
- For more information, see [http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html](http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* (E) (NIAID) (ARRA)

### 2009 H1N1—Responding to Pandemic Influenza:

NIH is engaged fully in the government-wide effort to understand the 2009 H1N1 virus and rapidly develop countermeasures. Activities are being conducted in NIH-supported research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as by industry partners and individual NIH grantees. NIH used its longstanding vaccine clinical trials infrastructure—notably, the network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates for safety and ability to induce protective immune responses, and to determine the appropriate dose and number of dosages. Because of increased resistance to existing antiviral therapeutics, NIH is working to develop the next generation of influenza therapeutics/antivirals. Three drugs now in clinical testing include a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. NIH will evaluate how well these candidate antiviral drugs block the 2009 H1N1 strain and will screen other compounds for activity against the virus. NIH also is developing diagnostic platforms that can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. NIH is accelerating development of these platforms to provide improved diagnostics for 2009 H1N1 influenza. In addition, enrollment is complete for an NIH pandemic
influenza H1N1 DNA vaccine Phase I clinical trial that has begun, and NIH scientists are conducting basic research to develop universal influenza vaccines that can protect against multiple influenza strains.

- For more information, see [http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm](http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID)

**Preclinical Disease Models Informatics:** Preclinical research results derived from animal models are an essential element in the decisional process to determine whether a basic science discovery should be considered as a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool designed to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative (LAMHDI) will integrate data and information about animal models and make them available to health researchers. LAMHDI creators will develop a database and website designed to make it easier for the biomedical research community to locate, identify, apply, and build upon the most useful animal models for its research. The initiative grew out of the Animal Models: Informatics and Access meeting in August 2008. At this meeting, animal research and informatics experts explored ways to remove research barriers and to develop frameworks for effective computation on existing animal models data to facilitate medical progress. The $1.57 million NIH-funded project is supported by a contract to Turner Consulting Group, a strategy and information technology firm.

- (E) (NCRR)

**Strategies to Manage and Prevent Food Allergies:** Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow’s milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

- For more information, see [http://www3.niaid.nih.gov/topics/foodAllergy/default.htm](http://www3.niaid.nih.gov/topics/foodAllergy/default.htm)
Muscle Recovery After Exercise or Injury: NIH funds a robust research portfolio on a wide range of basic, translational, and clinical research projects in skeletal muscle biology and diseases. In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions in which exercise is known to be helpful, but not always practical. For example, researchers have identified two drugs that, in mice, seem to confer many of the healthful benefits of long-term exercise by giving the animals more fat-burning muscle and better endurance. Their discovery built on earlier, more basic research, which identified a protein that regulates several fat-burning genes in muscle cells. Other researchers, exploring the role of a protein found in immature muscle cells, discovered that creatine supplements taken by athletes play an important role in muscle repair. Elsewhere, at the University of Iowa’s Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, scientists have identified a disrupted molecular pathway that leads to fatigue after even mild physical exertion in mice with muscular dystrophy. Their study demonstrated that a signaling pathway that regulates blood vessel constriction in skeletal muscle after mild exercise is defective in mouse models for Duchenne muscular dystrophy and other myopathies. This finding may lead to treatments for the post-activity exhaustion that strikes many people who have neuromuscular disorders.

- For more information, see http://www.nih.gov/news/research_matters/august2008/08112008mouse.htm
- For more information, see http://www.nih.gov/news/research_matters/november2008/11032008neuromuscular.htm

Toward Better Treatment for Muscular Dystrophy: NIH is pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funded two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in FY 2008: the Boston Biomedical Research Institute, which seeks to identify biomarkers that can be used in preclinical studies and clinical trials of potential facioscapulohumeral muscular dystrophy (FSHD) therapies, and a center at the University of North Carolina at Chapel Hill, which is developing and testing gene therapies for Duchenne muscular dystrophy (DMD) and other muscle disorders. Collectively, the Wellstone centers program is designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4) and to serve as a national resource for the muscular dystrophy community through core facilities and training programs. NIH funds multiple approaches to therapeutic development through projects outside of the Wellstone program, including a robust portfolio on translational research in muscular dystrophy. Research currently is solicited in this area through two Funding Opportunity Announcements (FOAs) released in 2008: Exploratory/Developmental Projects for Translational Research in Neuromuscular Disease (R21) and the Cooperative Program in Translational Research in Neuromuscular Disease (U01). Previous FOAs on Translational Research in Muscular Dystrophy resulted in a number of funded projects in this area, including projects to develop small molecule drugs and to develop effective gene
therapy design and delivery approaches. Progress also is being made toward the GPRA goal to "advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013."

- For more information, see [http://www.wellstonemdcenters.nih.gov/](http://www.wellstonemdcenters.nih.gov/)
- For more information, see [http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html](http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html)
- For more information, see [http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html](http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* (E) (NINDS, NHLBI, NIAMS, NICHD) (COE, GPRA)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research* (E) (NINR, NIA, DPCPSI, FIC, NCCAM, NCI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies, enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- **Knockout Mouse Project (KOMP)—**A trans-NIH initiative to individually inactivate approximately 8,500 protein-coding mouse genes to better understand their genetic functions, which are, in many cases, very similar to human genes. High throughput production started in 2006, and international distribution of validated embryonic stem cell lines with specific knockouts from the KOMP Repository became fully operational in 2008. The KOMP is supported by 19 ICs and Offices.
- **Mutant Mouse Regional Resource Centers—**More than 1,700 mutant mouse lines, and 27,000 mutant embryonic cell lines, are available from the consortium, which comprises three centers across the United States.
- **Rat Resource and Research Center—**Acquisition and distribution of rat models increased dramatically in FY 2008, because of adaptation of novel technologies to make directed mutations.
Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists from across the United States and beyond, representing more than $700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.
Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates widely are used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. NIH support for the centers ensures that these specialized resources are available to the research community. Several NIH ICs provide funding to investigators for specific research projects that use NPRC resources, thus increasing the efficiency of projects involving use of nonhuman primates. For example, in FY 2008, more than 1,000 research projects and more than 2,000 investigators used the animals and other resources provided by the NPRCs. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development and testing of novel microbicides to prevent infection by HIV, the virus that causes AIDS, and testing of AIDS vaccine candidates.
- Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases.
- Development of the first nonhuman primate model of a neurodegenerative disease—Huntington's disease.

For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hypoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis,
Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.


For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp

For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA.
exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA. Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (I) (NIEHS)

**Experimental Therapeutics for Cancer:** The NCI Experimental Therapeutics Program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and leads, through a series of progressive steps, to first-in-human studies. The ultimate goal is to accelerate the translation of new oncology agents to the clinic.

- For more information, see [http://dctd.cancer.gov/About/major_initiatives_NExt.htm](http://dctd.cancer.gov/About/major_initiatives_NExt.htm)
- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI)

**Alzheimer's Disease Neuroimaging Initiative (ADNI):** ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in
use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

- For more information, see [http://www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NIA, NIBIB)

**Therapeutics for Rare and Neglected Diseases Program (TRND):** NIH is developing a congressionally mandated therapeutics development program for rare and neglected diseases. The ORDR will handle oversight and governance of TRND, and researchers will perform TRND’s laboratory work in a new facility administered by the intramural program of NHGRI. TRND will build upon the similarly structured NIH Chemical Genomics Center (NCGC). NCGC facilitates drug development from the basic research laboratory to the chemical probe stage, which is when researchers begin to lay the groundwork for intensive preclinical development of candidate drugs. Picking up where NCGC and other organizations leave off, TRND will concentrate its efforts on the preclinical stage of drug development. TRND’s aim will be to move candidate drugs forward in the drug development pipeline until they meet Food and Drug Administration (FDA) requirements for an Investigational New Drug (IND) application. Once TRND generates enough data to support an IND application for a candidate drug, it will be licensed to an experienced organization outside of NIH, such as a biotechnology or pharmaceutical company, for human testing and regulatory submission. TRND also will devote considerable resources to the repositioning or repurposing of approved products for use in rare and neglected diseases. Like NCGC, TRND will pull together researchers with expertise in a broad and diverse range of scientific disciplines and disease areas. Specifically, TRND will encourage investigators from both inside and outside of NIH, from the public, private, and nonprofit sectors, to submit projects for work within its intramural facility. This will create ongoing collaborations that will benefit researchers and, most importantly, patients with rare and neglected diseases. NIH ICs and Offices have recommended staff members with expertise and experiences in product development programs to serve on a Trans-NIH Staff Advisory Group that will provide ongoing consultation regarding the operation of TRND and help integrate TRND with related or complementary efforts in the NIH ICs. A second group providing input for TRND is the External Expert Panel comprised of experts in preclinical drug development and rare and neglected diseases from academia, industry, and patient advocacy communities.

- For more information, see [http://www.genome.gov/27531965](http://www.genome.gov/27531965)
- For more information, see [https://rarediseases.info.nih.gov/TRND/](https://rarediseases.info.nih.gov/TRND/)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E/I) (ODP/ORDR, NHGRI)

**Neurobiology of Pain in Sickle Cell Disease:** The past 35 years have produced a remarkable expansion in scientific understanding of the neurobiological basis of pain, yet none of this research has been specifically focused on sickle cell disease (SCD), one of the few human diseases associated with lifelong, often severe, pain. To address this gap, an NIH-sponsored working group brought together
researchers studying the neuroscience of pain and hematologists having a special interest in SCD. Participants identified an urgent need for multidisciplinary studies encompassing neurobiology, hematology, pharmacology, and psychology. Based on the working group findings, in November 2008, NIH issued a request for grant applications, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to support basic and translational studies on the distinctive aspects of pain syndromes in SCD.

- For more information, see [http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-008.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-008.html)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NHLBI, NINDS)

**NIH Guidelines on Ethical Issues Associated with Human Specimen and/or Data Collections:** Human specimen and/or data collections increasingly are important for advancing basic biomedical and behavioral research and translating discoveries into improved health care. While numerous regulations and policies apply to specimen and data research, there is no comprehensive Federal policy that covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens and/or data for research. To address this need, NIH is developing draft guidelines for human specimen and data collections conducted or supported by NIH. The guidelines address ethical issues, including informed consent, protection from research risks, withdrawal of specimens and data, as well as management, oversight, access, and dissemination. The draft guidelines are expected to be issued for public comment in late 2009.

- For more information, see [http://oba.od.nih.gov/policy/policy_issues.html#CRP_004](http://oba.od.nih.gov/policy/policy_issues.html#CRP_004)
- (O) (OSP/OBA)

**Molecular Profiling to Tailor Cancer Treatment:** Molecular profiling is a powerful tool for identifying tumor subtypes and guiding clinical decisions to optimize patient benefit. NIH programs in this area include the Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program, which is evaluating the clinical utility of molecular signatures and helping translate molecular data into improved patient management, and the Lymphoma/Leukemia Molecular Profiling Project. Several studies from these and other programs demonstrate the value of tailoring cancer treatment based on molecular characteristics of the patient and tumor. Gene expression profiling revealed distinct diffuse large B-cell lymphoma (DLBCL) subtypes, one of which exhibits activation of the pro-survival NF-κB pathway. A recent study confirmed that bortezomib, a drug that indirectly prevents NF-κB activation through proteasome inhibition, selectively enhances the effects of chemotherapy in this DLBCL subtype. A recent study revealed that head and neck squamous cell carcinomas (HNSCCs) associated with human papilloma virus (HPV)-16 are more responsive to treatment than HPV-negative HNSCCs. Results from a recent clinical trial indicate that advanced colorectal cancers should be tested for mutations in the KRAS gene. Patients with tumors housing KRAS mutations are unlikely to benefit from targeted therapies that block epidermal growth factor receptor activity and should thus be spared the side effects and costs associated with these drugs. SPECS researchers recently developed an assay to classify breast cancer molecular subtypes and showed that when used in combination with clinicopathologic parameters (e.g., stage, grade), the assay improved prediction of prognosis and chemotherapy benefit.

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

NIH Bench-to-Bedside Program: An intramural Bench-to-Bedside Program was established in 1999 to integrate the work of basic and clinical scientists on the NIH campus and to foster collaborations across Institutes. Since the program's beginning, more than 500 principal and associate investigators have collaborated on 152 funded projects with approximately $33 million distributed in total bench-to-bedside funding. The program scope broadened in 2006 to include partnerships between intramural and extramural programs as part of a broader NIH effort to reduce barriers between intramural and extramural communities. Four funding cycles have been completed successfully, with approximately 50 extramural institutions partnering on bench-to-bedside awards (15 of these are CTSA sites). Last year the program expanded to allow extramural investigators to initiate bench-to-bedside awards. The call for proposals invited extramural investigators to identify intramural partners to lead the study via the CTSA network. As NIH explores opportunities to promote expanded collaborations with extramural clinical researchers, governing entities are exploring stable funding for the Bench-to-Bedside Program. Also under consideration is the establishment of a grants-type mechanism for bench-to-bedside awards that would allow direct funding to intramural and extramural investigators and streamline funds distribution. This program has served as a successful model of an intramural initiative that has broadened to include extramural partnerships.

Clinical Research: Learning Which Interventions Work

Recovery After an Initial Schizophrenic Episode (RAISE): Significant impairment of social and vocational function is the norm in chronic schizophrenia, and while antipsychotic drugs remain effective, they are not able to restore skills and abilities lost to the illness. A person experiencing an initial
psychotic episode usually responds well to antipsychotics and, unlike chronically ill patients, may recover completely from that first episode. NIH will fund an initiative to determine whether function could be preserved and disability forestalled after an initial schizophrenic episode with an intense and sustained pharmacological, psychosocial, and rehabilitative intervention. A single project will be supported to: (1) test the feasibility of recruiting and retaining newly diagnosed patients in a longitudinal trial; (2) develop the treatment model—a mix of pharmacological, psychological, and rehabilitative interventions—that is most likely to preserve function and maintain patient participation; and (3) determine the nature of the control intervention. This initiative will set the stage for a large-scale, definitive, randomized clinical trial.

- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIMH) (ARRA)

**Clinical Trials Networks for the Treatment of Mental Disorders:** NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial, which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

- For more information, see [http://www.clinicaltrials.gov/show/NCT00667745](http://www.clinicaltrials.gov/show/NCT00667745)
- For more information, see [http://www.clinicaltrials.gov/show/NCT00590863](http://www.clinicaltrials.gov/show/NCT00590863)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIMH)

**Advances in Mental Health Treatment Development:** NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- **Novel NeuroAIDS Therapies:** Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.

- **Innovative Approaches to Personalizing the Treatment of Depression:** NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.

- **Fast-acting Depression Treatments:** Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second
accuracy of magnetoencephalography. Depressed patients showed increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*.
- (E/I) (NIMH)

**Functional Gastrointestinal (GI) Disorders:** NIH is leading a number of initiatives to improve the diagnosis and treatment of functional GI disorders. The Gastroparesis Clinical Research Consortium (GpCRC) performs clinical, epidemiological, and therapeutic research to improve treatment of patients with gastroparesis (inability to move food properly from the stomach through the digestive system). Ongoing GpCRC studies include the Gastroparesis Registry and a multicenter, randomized clinical trial testing the use of nortriptyline (a tricyclic antidepressant) for treatment of gastroparesis. The use of antidepressants for the treatment of functional dyspepsia (indigestion) is being tested in the Functional Dyspepsia Treatment Trial; the study also aims to identify genetic markers associated with improved treatment outcomes. Additional NIH-sponsored clinical studies are testing the benefit of short-term cognitive-behavioral treatment for irritable bowel syndrome (IBS) and evaluating methods for diagnosing and treating Sphincter of Oddi Dysfunction, a disorder that results in bouts of abdominal pain from spasms of biliary and pancreatic valves. In addition, NIH provides continued support for the Center for Neurovisceral Sciences and Women's Health at UCLA, which conducts basic and clinical research on how the brain and digestive system communicate and how alterations in this communication result in IBS and other disorders. These initiatives will reduce the physical and psychosocial burdens associated with functional GI disorders.

- For more information, see [http://clinicaltrials.gov/ct2/show/NCT00398801](http://clinicaltrials.gov/ct2/show/NCT00398801)
- For more information, see [http://clinicaltrials.gov/ct2/show/NCT00765895](http://clinicaltrials.gov/ct2/show/NCT00765895)
- For more information, see [http://clinicaltrials.gov/ct2/show/NCT00248651](http://clinicaltrials.gov/ct2/show/NCT00248651)
- For more information, see [http://clinicaltrials.gov/ct2/show/NCT00738920](http://clinicaltrials.gov/ct2/show/NCT00738920)
- For more information, see [http://clinicaltrials.gov/ct2/show/NCT00688662](http://clinicaltrials.gov/ct2/show/NCT00688662)
- For more information, see [http://www.cns.med.ucla.edu](http://www.cns.med.ucla.edu)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK, NCCAM, ORWH)

**Phase II Clinical Trials of Novel Therapies for Lung Diseases:** Better treatments and diagnostic procedures are needed for lung diseases and sleep disorders. Although the results of basic research studies in cells, tissues, and animal models; investigations of biomarkers; and functional genomics have improved understanding of the pathogenesis of lung diseases and sleep disorders and suggested treatment targets, human testing often has not kept pace with the basic science advances. A recent solicitation encourages Phase II clinical trials to provide high-quality, proof-of-concept data to justify larger clinical efficacy trials. To foster collaborations between basic and clinical researchers and to obtain mechanistic understanding of new treatment approaches, each project is to include one interventional clinical trial led by a clinical investigator and at least one basic ancillary research study that is tightly related to the clinical question and led by a basic researcher. It is expected that four to six
awards will be made in FYs 2010 and 2011.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-003.html
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NHLBI)

**Obstructive Sleep Apnea Treatment Trials:** In 2009, NIH completed two prospective, randomized, double-blinded, sham-controlled multicenter evaluations of nasal continuous positive airway pressure (CPAP) as a first-line treatment for obstructive sleep apnea (OSA). OSA is characterized by brief episodes of airway obstruction that prevents air from reaching the lung and disturb sleep. It is the single most pervasive airway disorder and is associated with a greater risk of behavioral impairment, hypertension, stroke, diabetes, and all-cause mortality. The $14 million Apnea Positive Pressure Long-Term Efficacy Study (APPLES) was launched in September 2002 to determine whether CPAP therapy, compared with placebo, alleviates debilitating cognitive impairment associated with OSA. More than 1,100 OSA cases were studied over a period of 6 months using a battery of behavioral and sleep tests to assess changes in cognitive ability, mood, sleepiness, and quality of life. The $3 million CATNAP study was launched in August 2003 to assess the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. It studied 200 cases of mild OSA in which participants exhibited significant sleepiness. Findings from APPLES and CATNAP that are to be reported in 2010 will be the first evidence from U.S.-based clinical trials to guide health care providers in determining who should be evaluated and treated and what behavioral benefits can be expected.

- For more information, see https://apples.stanford.edu
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NHLBI)

**The Osteoarthritis Initiative:** A limited number of therapies exist for osteoarthritis (OA) treatment. Most only relieve pain and reduce disability; none slows or halts disease progression. One barrier to the development of drugs that block the underlying causes of OA symptoms is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, NIH—with input from FDA—partnered with private sponsors to create the Osteoarthritis Initiative (OAI). When complete, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. All data will be freely available to researchers worldwide, who can develop hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease development and severity. Scientists also can use the OAI to identify potential disease targets and to develop tools for measuring clinically meaningful improvements. The OAI originally was to receive funding through FY 2009, during which time investigators would collect survey, clinical, and image data and biological samples from approximately 4,800 people at baseline, 12-, 24-, 36-, and 48-month time points. NIH extended the study to include 72- and 96-month data. By the end of FY 2009, more than 1,350 researchers from 54 countries had registered to access OAI data. A total of 4,100 clinical datasets have been downloaded. In FYs 2008 and 2009, more than 18 articles using OAI data were accepted for publication in peer-
reviewed journals.

- For more information, see [http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative](http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIAMS, NCCAM, NCMD, NIA, NIBIB, NIDCR, ORWH) (GPRA)

**Progress Toward Immune Tolerance:** Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the-art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

- For more information, see [http://www.immunetolerance.org/](http://www.immunetolerance.org/)
- This example also appears in Chapter 2: Autoimmune Diseases and Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIAID, NIDDK)

**Transforming TB Research:** Diagnosis, treatment, and control of tuberculosis (TB) increasingly are complicated by the HIV/AIDS co-epidemic and the emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. NIH is pursuing six critical areas for additional investigation: (1) new TB diagnostic tools; (2) improved therapies for all forms of TB; (3) basic biology and immunology of TB; (4) MDR TB and XDR TB epidemiology; (5) clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and (6) TB prevention, including vaccines. Recent NIH advances in TB research include:

- Two FDA-approved drugs are found to work in tandem to kill laboratory models of *Mycobacterium tuberculosis* (Mtb) strains, the bacterium that causes TB. The drugs—meropenem and clavulanate—are used to treat other bacterial diseases. A clinical trial is being developed to test the combination in people who have XDR TB.
- New information on the pharmacology of existing and new anti-TB compounds may facilitate the development of improved treatment regimens for adults and children.
- Clinical trials have shown that the immune systems of children who are HIV-infected do not respond well to the current TB vaccine, BCG.
- Clinical trials also have shown that mortality among TB patients coinfected with HIV is reduced drastically when antiretroviral therapy is provided at the same time as TB therapy. Additional studies are underway to determine optimal strategies for the prevention, treatment, and
diagnosis of TB in the setting of HIV infection.

Several NIH-supported academic institutions, public-private partnerships, and commercial entities are developing rapid tests for early detection of all forms of TB, including MDR and XDR TB.

- For more information, see [http://www3.niaid.nih.gov/topics/tuberculosis](http://www3.niaid.nih.gov/topics/tuberculosis)
- This example also appears in Chapter 2: Infectious Diseases and Biodefense
- (E/I) (NIAID)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

- For more information, see [http://www.nida.nih.gov/scienceofaddiction/](http://www.nida.nih.gov/scienceofaddiction/)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System, Chapter 2: Chronic Diseases and Organ Systems and Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NIDA)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention deficit/hyperactivity disorder [ADHD])
and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

- For more information, see [http://www.drugabuse.gov/CTN/protocol/0028.html](http://www.drugabuse.gov/CTN/protocol/0028.html)
- For more information, see [http://www.drugabuse.gov/CTN/protocol/0029.html](http://www.drugabuse.gov/CTN/protocol/0029.html)
- For more information, see [http://www.nida.nih.gov/ResearchReports/comorbidity](http://www.nida.nih.gov/ResearchReports/comorbidity)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIDA, NIAAA, NIMH)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH’s collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain’s reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person’s genes.

- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIDA) (GPRA)

Comparative Effectiveness of Treatments for Common Childhood Eye Disorder: Convergence insufficiency (CI) is a relatively common vision problem that develops in childhood in which the eyes do not naturally turn inward when focusing on a close-up visual target. Symptoms include eye strain, blurred vision, headaches, and discomfort. CI can adversely affect reading ability and reading comprehension and can have a serious impact on an individual’s performance in school, career, and quality of life. Eye care professionals treat CI with various forms of eye exercises, done at home or in the office of a trained therapist, that require children to sustain focus
on nearby objects. The Convergence Insufficiency Treatment Trial (CITT) compared the effectiveness of these therapies. Results indicate that the most popular treatment, known as home-based pencil push-up therapy, was no more effective in improving patient's symptoms than a placebo therapy. However, 73 percent of children assigned to a regimen of intensive, office-based therapy combined with home reinforcement did improve significantly compared to the placebo group. Other commonly prescribed home-based regimens also showed some benefit but were only about half as successful as office-based therapy with home reinforcement. Although home-based treatments for CI are appealing because of their simplicity and low cost, these results indicate that office-based treatment combined with home reinforcement is more effective in helping children to achieve normal vision and reducing symptoms.

• For more information, see http://archopht.ama-assn.org/cgi/content/full/126/10/1336
• This example also appears in Chapter 2: Life Stages, Human Development, and Rehabilitation

NIH Establishes Neuro-Ophthalmology Clinical Research Network: The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network was established in spring of 2009 to investigate disorders that bridge neurology and ophthalmology and that often are difficult to diagnose and treat. The Network involves more than 200 community and academic practitioners. This consortium will provide a unique opportunity to recruit and study hard-to-find patients to evaluate risks, diagnoses, and treatment options that could not be accomplished without a coordinated effort. The first clinical trial funded under this network will be the Idiopathic Intracranial Hypertension (IIH) Treatment Trial. IIH typically occurs in women of childbearing age. Obesity increases the risk 20-fold. IIH is characterized by an increase in intracranial pressure resulting in blurred vision, double vision, and permanent vision loss. This trial will compare the additional benefit of acetazolamide (a diuretic) added to a low-sodium, weight reduction diet in newly diagnosed patients. Future planned studies include comparing treatments for ocular manifestations in Graves' disease, an autoimmune disorder that causes hyperthyroidism, estimated to affect 2 percent of all women between the ages of 20 and 40. Patients with Graves’ can develop protrusion of the eye balls and optic nerve damage. A network of researchers provides valuable expertise and widespread recruitment capabilities for studies of rare disorders.

• This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System

Comparative Effectiveness Study Finds Laser Treatment Preferable in Diabetic Macular Edema: The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to conducting multicenter clinical research for diabetic retinopathy and associated conditions. The DRCR.net was formed in September 2002 and currently includes 199 participating sites with more than 670 physicians throughout the United States. About 45 percent of the 18 million Americans diagnosed with diabetes have visual disorders such as macular edema. This occurs when the central part of the retina called the macula swells in diabetics—possibly leading to blindness. Laser treatment to reduce swelling has been the standard of care. However, early reports of success in treating diabetic macular edema with a corticosteroid, triamcinolone, have led to its widespread use. A DRCR clinical trial found that laser therapy is more effective and has far fewer side effects than intraocular injections of triamcinolone in treating diabetic macular edema. In the corticosteroid-treated group, 28 percent
experienced substantial vision loss as compared to 19 percent in the laser-treated group. Surprisingly and unexpectedly, vision improved in about one-third of the eyes treated with laser therapy. Results of this study confirm the preferential use of laser treatment for diabetic macular edema.

  PMID: 17698196. PMCID: PMC2245885.
  For more information, see [http://public.drcr.net/](http://public.drcr.net/)
  This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*

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**Progress in Parkinson's Disease Research:** For the past 7 years, NIH actively has been engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial cofunded by NIH and the Veterans Administration published its finding that Deep Brain Stimulation is more effective than standard drug therapy for Parkinson's disease but also carries a higher risk of adverse events. NIH also has begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

- For more information, see [http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm](http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm)
- For more information, see [http://www.parkinsontrial.ninds.nih.gov/index.htm](http://www.parkinsontrial.ninds.nih.gov/index.htm)
- For more information, see [http://www.ninds.nih.gov/udall_centers_evaluation](http://www.ninds.nih.gov/udall_centers_evaluation)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*

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**Clinical Research and Trials in Neurological Disease:** NINDS funds more than 1,000 extramural clinical research studies. Clinical researchers are studying, for example, disease mechanisms, risk factors that contribute to health disparities, brain imaging, and genes that predispose to disease as well as conducting multisite clinical trials that test the safety and efficacy of new prevention strategies and treatments or compare existing interventions. In the past year, for example, an NICHD/NINDS clinical trial reported that a drug commonly used to delay labor can prevent cerebral palsy in some circumstances, and a Veterans Administration/NINDS trial demonstrated that deep brain stimulation, a surgical intervention, is more effective than drug treatment at improving movement and quality of life for many people who have Parkinson's disease, but carries some risks. Among trials now underway, researchers are testing interventions to protect the brain following traumatic brain injury, to prevent stroke, to slow the progression of neurodegenerative diseases, and to treat multiple sclerosis. An independent study contracted by NINDS found that NINDS clinical trials which cost $335 million over 10 years provided benefits that exceeded $15 billion and added 470,000 healthy years of life to people in the United States. With guidance from an expert strategic planning panel, NINDS is continuing to improve the efficiency and payoff of the clinical trials program.
Research on Rare Neurological Disorders: NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system, while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. NIH reissued a Funding Opportunity Announcement (FOA) for new and renewal applications to continue the Rare Diseases Clinical Research Network (RDCRN), which funds collaborative clinical research consortia focused on rare diseases. NINDS will oversee the network's Data Management and Coordinating Center, and several of the consortia to be funded through this program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system. Through the NINDS translational research program, NIH supports milestone-driven therapy development for rare neurological diseases. Two funded projects, in Batten disease and Niemann-Pick disease, are nearing investigational new drug approval from FDA to conduct clinical trials, and a newly awarded project focuses on gene therapy approaches for the lysosomal storage disorders Tay-Sachs, San Fillipo, and Sandhoff disease. NIH also continues to support and encourage research to understand and treat Ataxia-telangiectasia and dystonia (including rare dystonias) through separate FOAs issued in collaboration with patient organizations.

- For more information, see [http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html)
- For more information, see [http://www.ninds.nih.gov/research/translational/Coop Tran_Res.htm](http://www.ninds.nih.gov/research/translational/Coop Tran_Res.htm)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System
- (E) (NINDS, NICHD)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports eight SPOTRIAS sites that have made substantial progress, including impressive increases in tPA use; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 951 individuals with acute stroke into treatment protocols; the management of 20 early-phase clinical trials; and the training of 79 research fellows.

- For more information, see [http://www.spotrias.com](http://www.spotrias.com)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System
- (E, I) (NINDS)

Clarification of Optimal Anticoagulation Through Genetics (COAG): NIH has launched the COAG trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin. The most commonly used oral anticoagulant in the United States, warfarin is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes. The drug is challenging for doctors to prescribe...
because the ideal dosage can vary widely from one person to another. Getting the wrong amount of warfarin can be dangerous—if the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The COAG study will determine whether knowledge about some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning warfarin treatment. The knowledge gained in COAG will make significant scientific contributions to several medical specialties as well as the field of pharmacogenetics and personalized medicine.

For more information, see [http://www.clinicaltrials.gov/ct2/show/NCT00839657](http://www.clinicaltrials.gov/ct2/show/NCT00839657)
For more information, see [http://coagstudy.org](http://coagstudy.org)

**Multiple Sclerosis Research:** Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

For more information, see [http://clinicaltrials.gov/ct2/show/NCT00211887](http://clinicaltrials.gov/ct2/show/NCT00211887)
For more information, see [http://clinicaltrials.gov/ct2/show/NCT00325988](http://clinicaltrials.gov/ct2/show/NCT00325988)
For more information, see [http://clinicaltrials.gov/ct2/show/study/NCT00950248](http://clinicaltrials.gov/ct2/show/study/NCT00950248)
This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Autoimmune Diseases
(E, I) (NINDS)

**Studies of Diabetes in Youth:** NIH and CDC support the SEARCH for Diabetes in Youth study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk
for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, which is comparing three different treatment strategies for children with the disease.

- For more information, see [http://www.searchfordiabetes.org/](http://www.searchfordiabetes.org/)
- For more information, see [http://www.todaystudy.org/index.cgi](http://www.todaystudy.org/index.cgi)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NIDDK, CDC)

**Preclinical and Clinical Research on Type 1 Diabetes:** NIH's Type 1 Diabetes TrialNet is an international network that tests strategies for prevention and early treatment of type 1 diabetes. TrialNet recently found that the drug rituximab delayed progression of type 1 diabetes in newly diagnosed patients. To identify environmental triggers of type 1 diabetes, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. TEDDY is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers. NIH's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients begin intensive therapy as early as possible. To help patients achieve good glucose control, new initiatives focus on clinical and behavioral research related to new technologies for glucose control and insulin delivery (e.g., artificial pancreas technologies). NIH also supports research on islet transplantation through the Clinical Islet Transplantation Consortium. To provide resources for preclinical development of agents to test in clinical trials, NIH established the Type 1 Diabetes—Rapid Access to Intervention Development program.

- For more information, see [http://www.diabetestrialnet.org](http://www.diabetestrialnet.org)
- For more information, see [http://www.teddystudy.org](http://www.teddystudy.org)
- For more information, see [http://www.citisletstudy.org/](http://www.citisletstudy.org/)
- For more information, see [http://www.t1diabetes.nih.gov/T1D-RAID/](http://www.t1diabetes.nih.gov/T1D-RAID/)
- This example also appears in Chapter 2: Autoimmune Diseases
- (E) (NIDDK, NCCAM, NCI, NIAID, NICHD)

**Obesity, Inflammation, and Fat Cell Biology:** NIH supports diverse research on fat (adipose) tissue, including studies that examine the relationship between obesity and inflammation in white adipose tissue, as well as research on another type of fat tissue, brown fat. In obese patients, lipid laden white adipose tissue secretes a number of proinflammatory molecules such as TNF-alpha (as well as other types of signaling molecules associated with insulin resistance). Chronic low-grade tissue inflammation observed in obese individuals has been linked to type 2 diabetes and cardiovascular
disease risk. An NIH-funded, multicenter research study called Targeting INflammation using SALsate for Type-2 Diabetes (TINSAL-T2D) has been initiated to determine whether salsalate, an inexpensive anti-inflammatory drug, could be a new treatment option for patients with type 2 diabetes. A different avenue of research led to the surprising discovery of metabolically active brown adipose tissue in adult humans. While white fat cells store fat, brown fat cells burn fat to generate heat, and were once thought to exist only in infants. Research on brown fat in adult humans, as well as studies in animal models, may lead to novel strategies for obesity therapy.

- For more information, see http://tinsalt2d.org/
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIDDK)

Look AHEAD (Action for Health in Diabetes): This NIH-led, multicenter, randomized clinical trial is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Results from the first year of the study showed that participants in the ILI group achieved clinically significant weight loss; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in "health-related quality of life" and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose, as compared to a control group receiving diabetes support and education. As another major point for health outcome measurement, the study recently completed 4 years of intervention and follow-up. In the coming years, continued follow-up of the Look AHEAD participants will show whether the ILI can reduce the incidence of heart attack and stroke and improve other health-related outcomes in this population. These findings will have important implications for treating type 2 diabetes.

- For more information, see http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalTrials/Patients/ClinicalResearchLookahead.htm
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 2: Minority Health and Health Disparities
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes: While health care advances continue to transform previously acute/fatal conditions into chronic conditions and individual life expectancy is increasing, issues of quality of life have become ever more important. Studies focusing on the management of disease- and treatment-related symptoms have demonstrated the capacity for behavioral strategies to mitigate effects of symptoms and contribute to improving short- and long-term patient outcomes. For example, behavioral strategies have been shown to improve patient outcomes across various diseases including diabetes, irritable bowel syndrome, and asthma. In recognition of the need for new behavioral strategies to manage chronic illness, NIH has established a goal of developing and testing behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes by 2012. Beginning in FY 2008, progress toward achieving this goal has been updated annually in the Online Performance Index section of NIH’s portion of the President’s budget submission to Congress.
Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

Intervention Reduces Risky Sexual Behavior Among Homeless HIV-Infected Adults: HIV infection in the United States is found more commonly among populations with significant life stressors, such as homelessness and drug use. An NIH-funded program (the Healthy Living Program) already shown to reduce risky sexual and substance abuse behavior among HIV-infected adults also appears to be effective in improving the lives of HIV-infected homeless or near-homeless adults. The program consisted of three intervention modules of five sessions each, designed to help participants reduce risky sexual behaviors and drug use, improve their quality of life, and sustain healthy behaviors. Compared with a control group who did not receive the Healthy Living Program intervention, individuals who were homeless or near-homeless in the 3 years prior to and during the study and who participated in the intervention engaged in 34 percent fewer risky sexual acts and 72 percent fewer sexual encounters with partners who were not infected with HIV or were of unknown HIV status. The study's results highlight the importance of programs designed to prevent or reduce the spread of HIV among people in high-risk populations. They also indicate that intervention programs focusing on skills development and including the physical and mental health needs of participants, are more likely to succeed than programs focusing only on reducing HIV transmission.
Research Initiatives to Study Suicidality and Mental Health Needs of U.S. Army Soldiers and Returning Combat Veterans: The high rates of mental health and behavioral adjustment problems among recent U.S. military combat veterans, and the increasing rates of suicide among Army soldiers, are of growing concern. To address these issues, NIH is collaborating with the U.S. Army to evaluate selected groups of soldiers across all phases of Army service, including entry-level training and service, pre-deployment training, deployment and noncombat assignments, post-deployment, and post-separation reintegration to civilian life. The study's intent is to identify modifiable risk and protective factors, as well as moderators, of suicide-related behaviors. NIH also is launching a study of the impact of existing national, state, and local community-based programs addressing the adjustment and mental health needs of recent combat veterans, including returning National Guard, Army Reserve, and newly separated active duty personnel. This initiative will produce new information concerning effective strategies for fostering successful transition from combat to civilian roles for returning service members.

- For more information, see [http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html)
- This example also appears in Chapter 3: Epidemiological and Longitudinal Studies

Unexpectedly, Corneas from Older Donors Found Suitable for Transplantation: Light first enters the eye through the crystal clear cornea and is focused on the retina. Each year approximately 33,000 Americans undergo corneal transplants to replace diseased corneas that either become cloudy or no longer properly focus light, causing severe visual impairment. Corneal transplants are among the most common and successful transplantation procedures in medicine. Availability of donor tissue is key to this sight-restoring procedure. However, many eye banks refrain from harvesting tissue from donors over age 65 because of uncertainty about the integrity of older corneas. Newly instituted FDA regulations to further safeguard transplant recipients and the common use of LASIK surgery to correct refractive errors—which renders corneal tissue unusable for transplantation—could significantly limit future tissue supplies. The Cornea Donor Study (CDS) found that corneal transplants using tissue from donors ages 66-75 have similar success rates to those using tissue from donors ages 12-65. Based on these findings, the study authors recommend that the age limit for donor tissue could be safely expanded to age 75. The CDS study gives eye banks, transplant surgeons, and patients confidence in the use of older donor tissue, and should help eye banks keep pace with the demand for corneal tissue.

- For more information, see [http://www.ophsource.org/periodicals/ophtha/article/PIIS0161642008000055/fulltext](http://www.ophsource.org/periodicals/ophtha/article/PIIS0161642008000055/fulltext)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems

Evidence-Based Review Program: In FY 2001, NIH received a congressional mandate to review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. NIH responded by developing an evidence-based review program using the Evidence-Based Practice Centers Program established by the Agency for Healthcare Research and Quality to conduct systematic reviews of the scientific literature and prepare reports of their findings. These reports have resulted in the publication of a number of articles in the peer-reviewed literature, and have helped NIH make decisions on research priorities in these areas. NIH ICs have found these reports invaluable in presenting what is and is not known in a research area, thus laying a sound foundation for identifying
gaps in knowledge and providing a strong scientific basis for the development of a research agenda and for informing health policy decisions. Currently, NIH is sponsoring an evidence report on Vitamin D and Calcium: Systematic Review of Health Outcomes that will be considered by the IOM committee established to assess current relevant data and update as appropriate the Dietary Reference Intakes for vitamin D and calcium.

- For more information, see [http://ods.od.nih.gov/Research/EvidenceReports.aspx](http://ods.od.nih.gov/Research/EvidenceReports.aspx)
- (E) (ODP/ODS)

**ClinicalTrials.gov:** ClinicalTrials.gov was significantly modified during FY 2008-2009 to respond to new clinical trial registration and results reporting requirements established by the FDA Amendments Act of 2007 (PL 110-85). The existing registry was expanded to accommodate the submission of more information about a larger number of trials, including those trials of FDA-regulated drugs, biological products and devices that now are required to register. In addition, NIH developed and implemented results modules to accept and display to the public summary results information, including adverse event information from registered trials. Mandatory reporting of results began in September 2008, with mandatory submission of adverse event information following in September 2009. During FYs 2008-2009, more than 34,000 trials were newly registered with ClinicalTrials.gov, raising the total number of registered trials to 60,000. In addition, summary results of more than 830 clinical trials were submitted and made available at ClinicalTrials.gov, with the rate of results submission approaching 200 trials per month by the end of FY 2009. To solicit input on issues to be considered in rulemaking for further expansion of ClinicalTrials.gov, a public meeting was held in April 2009; more than 200 participants attended the meeting, and more than 70 written comments were submitted to a public docket.

- This example also appears in Chapter 3: Disease Registries, Databases, and Biomedical Information Systems
- (I) (NLM)

**Multicenter AIDS Study (MACS) Small Grant Opportunity:** MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

- This example also appears in Chapter 2: Infectious Diseases and Biodefense and Chapter 3: Epidemiological and Longitudinal Studies
- (E) (NIAID, NIDA, NIMH)

**A Variety of Approaches Help Children Overcome Auditory Processing and Language Problems:** Almost 7 percent of school-age children have difficulties learning and using language. Childhood language impairments can have lifelong effects on an individual's social life, academic career, and job aspirations. Each year, more than 1 million public school children receive interventions to address their language impairments. One very popular intervention is a commercially available software program called Fast ForWord Language (FFW-L; Scientific Learning Corporation, 1998). NIH-
supported scientists conducted a randomized controlled trial of more than 200 children with language impairments, to assess whether those who used FFW-L had greater improvement in language skills than those who used one of two other methods, plus an active control group. The children in all three intervention groups demonstrated statistically significant improvement in both auditory processing and language skills. Thus, FFW-L did not provide a significant advantage over other types of interventions delivered in a similar intensive manner. Surprisingly, children in the active control group, which received individualized attention, instruction, and computerized testing on academic subjects but did not receive language intervention, also demonstrated significant improvement in auditory processing and language skills. This study demonstrated that all four methods improved the children's auditory processing and language skills. The data suggest that intensive programs focusing individualized attention on children with language impairments can improve language skills and preempt lifelong communication difficulties.

- For more information, see [http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm](http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm)
- This example also appears in Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NIDCD, NICHD)

**Liver Disease Research:** NIH supports clinical research to address the spectrum of liver diseases. The Nonalcoholic Steatohepatitis Clinical Research Network conducts placebo-controlled clinical trials of treatments for this condition, both in adults given pioglitazone or vitamin E, and in children given metformin or vitamin E. The Hepatitis B Clinical Research Network will conduct clinical trials to evaluate the effectiveness of different treatments and learn more about the natural history of this disease. The Childhood Liver Disease Research and Education Network combines and expands previous consortia focused on biliary atresia and cholestatic liver disease. This new network will foster discovery of new diagnostic and treatment options for children with these diseases or who undergo liver transplantation, and support research training in rare pediatric liver diseases. Plans for another clinical network are beginning with a study to test whether immunosuppression minimization would be safe and thus beneficial in children several years after liver transplantation. The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. Current studies are testing potential therapies to improve survival. For example, results of a clinical trial to test intravenous N-acetylcysteine as a treatment for nonacetaminophen-related acute liver failure showed significant improvement in transplant-free survival in individuals who received therapy early in the course of their acute liver failure. The Drug-Induced Liver Injury Network conducts research aimed at understanding, diagnosing, and ultimately preventing liver toxicity due to drugs or complementary and alternative medicines. Future efforts of this network will focus on identifying genetic risk factors for drug-induced liver toxicity.

- For more information, see [http://www.jhucc.com/nash/](http://www.jhucc.com/nash/)
- For more information, see [http://dilin.dcri.duke.edu/](http://dilin.dcri.duke.edu/)
- For more information, see [http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html](http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html)
- For more information, see [http://www.palfstudy.org/](http://www.palfstudy.org/)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) (NIDDK, FDA, NCI, NICHD) (GPRA)

**OHARA: The Oral HIV/AIDS Research Alliance:** At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS
Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

- For more information, see http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3
- For more information, see http://www.nidcr.nih.gov/Research/DER[IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm
- For more information, see http://aactg.org/about-aactg
- For more information, see http://www.who.int/hiv/data/en/
- For more information, see http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main
- This example also appears in Chapter 2: Infectious Diseases and Biodefense and Chapter 3: Epidemiological and Longitudinal Studies
- (E) (NIDCR, NIAID)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the New England Journal of Medicine. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents, NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

- For more information, see http://win.niddk.nih.gov/publications/labs.htm
- For more information, see http://www.nih.gov/news/pr/apr2007/niddk-16.htm
Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

- For more information, see [http://www.uitn.net/](http://www.uitn.net/)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) of 10 academic clinical centers, launched in 2002, evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, which can be indicative of asthma in children under age 3. ICAC has extended the study to follow all participant children to age 7, when the diagnosis of asthma can be definitive. Researchers hope to identify immunologic characteristics that will predict the development and severity of asthma at a later age. ICAC researchers are conducting two clinical trials to determine the safety, dosing levels, and biologic activity of a potential new allergy immunotherapy for cockroach allergen, which ICAC studies previously found to be a major determinant of asthma severity among inner-city children. Finally, an ICAC clinical trial assessed the benefit of using exhaled nitric oxide (NO) as a marker for asthma management. Although the study reinforced the importance of the NIH asthma guidelines for disease control, it did not find that measuring exhaled NO provided any additional clinical benefit.

- For more information, see [http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm](http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
**Rural Latino Preschooler's Oral Health: Intersections among Family, Community, Providers and Regulators:** Latino children experience among the highest prevalence of early childhood dental caries in the United States. Researchers explored the intersections among four societal sectors or contexts of care that potentially contribute to oral health disparities for low-income, preschool Latino children in rural California. The ethnographic investigation was conducted in a predominately Mexican-American agricultural community. Observations occurred in homes, community facilities, and dental offices, and were supplemented with in-depth interviews by trained anthropologists with key community informants and primary caregivers of children less than 6 years old. Factors that significantly intersected to produce or sustain poor oral health care for children follow. Caregivers did not always recognize signs of decay among their children, nor quickly respond unless children also complained of pain. Fluctuating eligibility for health insurance intersected with limited community infrastructure and civic amenities, including lack of public transportation, to create difficulties in access to care. Nonfluoridated bottled water often was consumed rather than tap water because of fears about potential pesticide pollution of the municipal water supply. Multiple dental visits caused parental hardship and occasionally resulted in the loss of the caregiver's job. Dental fear and poor provider-caregiver communication were exacerbated by a scarcity of dentists willing to serve rural low-income populations. Such empirical research related to newly emerging conceptual models is greatly needed. Understanding that multiple, intersecting factors at numerous levels will inform intervention research customized to the individual, community, and society.

- For more information, see [http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesChildren2to11](http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesChildren2to11)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*

**Alzheimer's Disease Cooperative Study (ADCS):** Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see [http://www.adcs.org/Default.aspx](http://www.adcs.org/Default.aspx)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
Interventions to RemEDIATE Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program’s primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.


This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 2: Life Stages, Human Development, and Rehabilitation

Comparative Effectiveness Study of Drugs for Age-Related Macular Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately $2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately $100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach $2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.


This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 2: Life Stages, Human Development, and Rehabilitation

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as
rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the
treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing
proof-of-concept for gene transfer as a viable therapy for eye disease.

Pmcid: PMC2567501.
- For more information, see http://www.pnas.org/content/105/39/15112.long
- For more information, see http://www.nei.nih.gov/lca/
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems and Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NEI)

Clinical Research Networks: Clinical research is essential for translating laboratory findings into
evidence-based interventions targeting an array of public health concerns. Many research programs
involve collaborative networks, drawing scientists together to bring the benefits of clinical research to
high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions.
Among such networks that have generated significant findings to advance medical practice and
improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network,
Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor
Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and
Children's Health Research.

- For more information, see http://www.bsc.gwu.edu/mfmu/index.html
- For more information, see https://neonatal.rti.org
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-002.html
- For more information, see http://www.cpccrn.org
- For more information, see http://www.pfdnetwork.org
- For more information, see http://www.tbi-ct.org/
- For more information, see http://gn.rti.org/about/index.cfm
- This example also appears in Chapter 2: Life Stages, Human Development, and Rehabilitation
- (E) (NICHD, FIC, NCCAM, NCI, NIDCR, ORWH)

Clinical Trials Network: NCI-supported clinical trials networks share resources and pool data to
promote and support the study of new cancer treatments, methods of cancer prevention and early
detection, and quality-of-life and rehabilitation issues. The 65 NCI-designated Cancer Centers serve as
a major platform for these trials. NCI is restructuring the Clinical Trials Enterprise. Initiatives include:
Standard Terms of Agreement for Research Trials, the Clinical Trials Reporting Program, correlative
studies (e.g., biomarkers, imaging, and quality-of-life studies) embedded in clinical trials, disease-
specific and patient advocate steering committees, and acceleration of translational research. The
Community Clinical Oncology Program recently stopped the Selenium and Vitamin E Cancer
Prevention Trial. Initial data analysis showed that selenium and vitamin E supplements, taken either
alone or together for an average of 5 years, did not prevent prostate cancer. Recent findings from NCI's
Cooperative Group Program include a gene abnormality that predicts childhood leukemia relapse, the
role of the ch14.18 monoclonal antibody in the treatment of high-risk neuroblastoma, and the
usefulness of CT colonography in detection of large adenomas and cancers. Year 2 accomplishments
of the NCI Community Cancer Centers Program include increased patient and physician involvement in
NCI-sponsored trials, new methods for tracking minority accrual, and improved specimen collection.
The Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR) is coordinating a
neurofibromatosis clinical trials program to develop effective therapies for this disease. The CCR also is
conducting trials for patients with androgen-independent and metastatic prostate cancer using anti-
angiogenic compounds as well as novel immunotherapies and immunologic strategies.

- For more information, see [http://restructuringtrials.cancer.gov/](http://restructuringtrials.cancer.gov/)
- For more information, see [http://prevention.cancer.gov/programs-resources/groups/copt/programs/about](http://prevention.cancer.gov/programs-resources/groups/copt/programs/about)
- For more information, see [http://www.cancer.gov/clinicaltrials/digestpage/SELECT/](http://www.cancer.gov/clinicaltrials/digestpage/SELECT/)
- For more information, see [http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group](http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group)
- For more information, see [http://ncccp.cancer.gov](http://ncccp.cancer.gov)
- For more information, see [http://content.nejm.org/cgi/content/full/359/12/1207](http://content.nejm.org/cgi/content/full/359/12/1207)
- For more information, see [http://ccr.cancer.gov](http://ccr.cancer.gov)
- This example also appears in Chapter 2: *Cancer*

### NIH Undiagnosed Diseases Program (UDP):
In May 2008, NIH launched a program to evaluate patients with disorders that have evaded a diagnosis. Often patients seek help from multiple physicians and other health care providers over many years without receiving a diagnosis. Using a unique combination of 35 NIH scientific and medical specialty experts, the UDP pursues three goals: To help patients with unknown disorders reach an accurate diagnosis, to discover new diseases that provide insight into human biology, and to reestablish the NIH CC as the referral Center for mystery diseases. In its first year, the UDP received more than 2,000 inquiries, with approximately half of them of neurological origin, and 100 of them pediatric. Of the 2,000 inquiries in the first year, 850 were followed up with submission of medical records; 450 of the applications to participate in the program were deemed inappropriate; and 158 cases were accepted into the program by 10 Institutes and Centers. The program is trans-NIH in scope. Senior attending physicians with many different medical specialties from NIH research Centers and Institutes contribute the expertise needed to achieve the goals of this clinical research program. Any longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of clinical interest.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) *(ODP/ORDR, CC, NHGRI, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIMH, NINDS, NINR)*

### Specialized Centers of Research (SCORs) on Sex and Gender Factors:
The SCORs on Sex and Gender Factors Affecting Women's Health provide an innovative and interdisciplinary approach to advancing research on the influence of sex and gender as it relates to health and disease. Each of these SCORs emphasizes research in an area of clinical importance to women's health. The 11 current SCORs, co-funded with five NIH ICs and the Food and Drug Administration, address sex/gender research in the areas of depression, pain, urinary tract infection, reproductive issues, substance abuse, and osteoporosis. An example of scientific advances includes the isolation of an estrogen receptor alpha signaling process that therapeutically could be downregulated to reduce the risk for obesity and type 2 diabetes in menopausal women. In 2009, the SCORs contributed 116 journal articles, 176 abstracts, and 63 other publications (reviews and book chapters) resulting from their research.

- For more information, see [http://orwh.od.nih.gov/interdisciplinary/SCORs.html](http://orwh.od.nih.gov/interdisciplinary/SCORs.html)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) *(ORWH, FDA, NIAMS, NICHD, NIDA, NIDDK, NIMH)*
Compliance with the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and investigator reporting of population data. Over the past 2 years, NIH has focused on analyzing and streamlining the data reporting process, reemphasizing the vital role of NIH staff to monitor adherence of the NIH Inclusion policy and management of grants, contracts, and cooperative agreements that involve human subjects research. The role of peer reviewers and investigators in meeting policy requirements continues to be stressed. NIH compiled the annual aggregate comprehensive reports: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research and the 2009 Biennial Report Certifying IC Compliance with the Inclusion Guidelines based upon IC Advisory Council reviews, as required by statute.

- For more information, see [http://orwh.od.nih.gov/inclusion.html](http://orwh.od.nih.gov/inclusion.html)
- This example also appears in Chapter 2: Minority Health and Health Disparities
- (E/I) (ORWH, OER, OIR)

Developing Biodefense Vaccines and Therapeutics: NIH is the lead Federal agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIAID is the lead Institute within NIH in this area. Counter measures against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation’s well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in countermeasures. To remedy this situation, NIH supports unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against diseases such as smallpox and botulism, as well as for infections with Ebola, Marburg, and West Nile virus infection. NIH advances include progress toward vaccines and/or therapeutics for anthrax, smallpox, and West Nile viruses. NIH supported development of a nonhuman primate model for plague; studies in the model have been completed for three licensed antibiotics for plague. In addition, advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.

- For more information, see [http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/](http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/)
- This example also appears in Chapter 2: Infectious Diseases and Biodefense
- (E/I) (NIAID)

NIEHS Clinical Research Unit: NIEHS focuses its research mission on environmental effects on human health, an area where human research data often are lacking. To improve the translation of basic research to human health, the NIEHS is expanding its Clinical Research Program (CRP). NIEHS has opened a new Clinical Research Unit (CRU) on the Research Triangle Park, NC, campus. The mission of the CRP is to translate basic laboratory findings to humans; study interactions between genetic susceptibility and environmental factors in the pathogenesis of complex human traits and diseases; and identify populations at risk and develop novel preventative and therapeutic strategies to combat human diseases. The CRU will provide support for the development of clinical research protocols; provide patient screening, recruitment and enrollment functions for NIEHS clinical studies;
provide basic sample processing support (e.g., clinical labs and cell isolation); and provide support for specialized clinical procedures and services with the ultimate vision of fostering substantial onsite clinical research activity. Examples of the kinds of studies that will be supported by the CRU include the following: collection of tissue and body fluid samples for ex vivo human studies; investigation of host response to environmental exposures; Phase I-II-III clinical trials; environmental intervention studies; and phenotyping of selected individuals from NIEHS research populations such as the Environmental Polymorphism Registry. The CRU will be an integral part of the NIEHS intramural research portfolio and will provide support to a substantial number of NIEHS scientists.

- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (I) (NIEHS)

**Putting Clinical Research Results into Practice**

**Genotyping Information for Use in Warfarin Therapy:** The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the Pharmacogenetics Research Network (PGRN), sponsors data-sharing consortia. In 2009, one of the consortia, the International Warfarin Pharmacogenetics Consortium (IWPC), completed its first project: Clinical and genetic data from more than 4,000 patients worldwide who received warfarin were assembled into a large dataset to create a universal dose algorithm that incorporated genetic factors along with clinical factors. This established a better method to calculate the initial dose of the anticoagulant, and NIH will use the information for a prospective clinical trial to determine the value of pre-prescription genotyping. Further genomic analyses of the warfarin data set are underway. Based upon the success in this endeavor, more consortia were created in 2009. The International Tamoxifen Pharmacogenetics Consortium (ITPC) was formed to gather genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects, and the International Severe Irinotecan Neutropenia Consortium (INSINC) was formed to assemble a large dataset to answer questions definitively relating to genetic effects on adverse outcomes of irinotecan therapy, and to provide tools for evaluating toxicity risk.

- For more information, see [http://www.nigms.nih.gov/Initiatives/PGRN](http://www.nigms.nih.gov/Initiatives/PGRN)
- For more information, see [http://www.pharmgkb.org/views/loadConsortia.action](http://www.pharmgkb.org/views/loadConsortia.action)
- This example also appears in Chapter 3: Genomics
- (E) (NIGMS, NCRR, NHLBI, NINDS) (GPRA)

**Workshop on Assessing Cost-Effectiveness in Clinical Research:** Cost-effectiveness analysis (CEA) has been an ongoing element of the NIH clinical research portfolio for many decades. It is a close relative of comparative effectiveness research and, as a tool, can be applied usefully to data from either efficacy or effectiveness studies. CEA accounts for a small but important proportion of overall NIH research expenditures, totalling $49 million in FY 2008. It comprises a relevant issue for scientists, health care providers, patients, families, and caregivers. In continuing its research tradition, in July of 2008, NIH hosted a workshop titled, "Integrating Cost-Effective Analysis into Clinical Research" in order to build a foundation for identifying interventions that will improve both health outcomes and the cost effectiveness of treatments. Building on workshop results, NIH issued the RFA "Incorporating Cost-Effectiveness Analysis into Factors Affecting Quality-of-Life Health Related Research (R01)" (RFA-NR-09-005). This Funding Opportunity Announcement solicits applications to
study the cost effectiveness of interventions that will improve health outcomes.

- For more information, see [http://www.ninr.nih.gov/NewsAndInformation/MeetingSummariesandReports](http://www.ninr.nih.gov/NewsAndInformation/MeetingSummariesandReports)
- For more information, see [http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-005.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-005.html)
- (E, O) (NINR, NCI, ODP/ODS, ODP/ORDR)

**NIH Consensus Development Program:** This program, administered by the Office of Medical Applications of Research (OMAR) within the Office of the Director, NIH, was established in 1977 as a mechanism to assess, translate, and disseminate the results of biomedical research. Since its inception, OMAR has conducted more than 120 Consensus Development Conferences, and 30 State-of-the-Science (formerly "Technology Assessment") Conferences. The program generates evidence-based statements addressing controversial issues in medicine and public health that are useful and relevant for health care providers, policymakers, patients, researchers, and the general public. The conferences are structured around key questions, including questions on the efficacy, risks, and clinical applications of a technology, along with current gaps in knowledge to help formulate directions for future research. For every conference, a systematic evidence review is performed through a partnership with the Agency for Healthcare Research and Quality to serve as the foundation upon which the conference will build. Experts in the field provide additional input and insights through several days of oral presentations. The conferences also contain sessions for public input and discussion. A multidisciplinary, nonadvocacy, independent panel free from scientific or financial conflicts considers all of this information, and then writes a statement answering the posed conference questions. Consensus and state-of-the-science statements are disseminated widely after the conference to either impact clinical practice—when evidence strongly supports the use (or avoidance) of a particular intervention—or to direct future research—when important gaps in knowledge have been identified. Upcoming conferences in 2010 include: Enhancing Use and Quality of Colorectal Cancer Screening; Lactose Intolerance and Health; Vaginal Birth After Cesarean: New Insights; Preventing Alzheimer's Disease and Cognitive Decline; and Inhaled Nitric Oxide Therapy for Preterm Infants.

- For more information, see [http://consensus.nih.gov/](http://consensus.nih.gov/)
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (ODP/OMAR)

**Family Satisfaction During Decisions to Withdraw Life Support:** Clinicians in the intensive care unit (ICU) often care for patients who are on several life support measures simultaneously. When such a patient is dying and the decision is reached to withdraw life support, these clinicians may make an imperfect compromise in seeking to balance the complex needs of the patient and the patient's family—they may remove the life support measures one at a time over a period of days, rather than withdrawing all at once. This practice, referred to as sequential withdrawal, may be relatively common, and may have a varying impact on the family's satisfaction with ICU care. The research team examined the life support withdrawal process for 584 patients who died in the ICU or within 24 hours of discharge from the ICU, and surveyed the family members regarding their perceptions of the care provided. When surveyed 1 to 2 months after the death of the patient, family members of patients who had a short ICU stay reported a lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended duration of the withdrawal. In addition, family satisfaction with care was higher if the patient was off the ventilator at the time of death. Withdrawal of
life support is a complex process that depends on patient and family characteristics; however, sequential withdrawal of life support is a frequent phenomenon that sometimes seems to be associated with family satisfaction.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR)

**Centers in Self-Management or End-of-Life Research:** Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, including more trained investigators and expanded institutional resources. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to serve as a nexus for the emergence of self-management and end-of-life research as interdisciplinary sciences. They will train investigators from multiple backgrounds and leverage collaborations to increase the quantity and quality of innovative, interventional research projects. To date, six grants have been awarded from this solicitation. These Centers focus on a variety of topics, such as the self-management of chronic illnesses in Hawaii, biobehavioral research in self-management of cardiopulmonary disease, evidence-based practice in the underserved, and end-of-life transition research.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR)

**Support for Research on the Dissemination, Implementation, and Operation of HIV Preventive Interventions:** NIH continues to support research on all aspects of HIV preventive interventions. While effective preventive interventions have been developed, there is a recognized gap between their development and their later uptake by community-level service providers. In FY 2008, NIH issued a funding opportunity announcement (FOA) to encourage research ensuring that these interventions are adopted and effectively implemented. The FOA invites applications for research projects that will enhance technology transfer, dissemination, implementation, and operational research related to evidence-based HIV preventive interventions. Staff from NIH and the Centers for Disease Control and Prevention collaborated in the development of this FOA by identifying research gaps and opportunities in these areas. Five categories of projects, in particular, were identified in which additional research activities could assist in the effective and efficient implementation of HIV preventive interventions: dissemination strategies, adoption of interventions, implementation fidelity and adaptation, intervention effectiveness, and sustainability of interventions.

- For more information, see [http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html](http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIMH, CDC, NICHD, NINR)

**Rapid HIV Testing Clinical Trial:** HIV testing is an important component of HIV prevention. To help prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to
making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. Still, little is known about whether offering testing in the absence of counseling influences patient acceptance or how they receive results. How and whether testing absent counseling influences HIV risk behaviors among those who are HIV negative also remains to be determined. Indeed, the Institute of Medicine has recommended comparison research to include significant prevention counseling as a key variable. In this regard, a randomized controlled clinical trial—taking place in NIH's Drug Abuse Treatment Clinical Trials Network—is recruiting individuals receiving drug abuse treatment to participate in a multicenter HIV testing and counseling study. The study will assess the relative effectiveness of on-site HIV rapid testing with brief, participant-tailored prevention counseling as compared with (1) on-site testing with information only and (2) referral for off-site HIV testing. HIV screening has important public health implications, recognized by the Centers for Disease Control and Prevention, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see [http://www.drugabuse.gov/about/organization/arp](http://www.drugabuse.gov/about/organization/arp)
- For more information, see [http://www.drugabuse.gov/CTN/protocol/0032.html](http://www.drugabuse.gov/CTN/protocol/0032.html)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*

**HIV Topical Microbicides:** Topical microbicides are small molecule prophylactic treatments to prevent the transmission and spread of HIV. Guided by the NIAID Topical Microbicide Strategic Plan, NIH is funding a number of microbicide research studies through the Microbicide Trials Network (MTN), the HIV Prevention Trials Network (HPTN), and the Microbicide Innovation Program (MIP). The microbicides under investigation are designed to prevent HIV transmission by killing or inactivating microbial pathogens, strengthening the body's normal defenses, blocking attachment of HIV to susceptible cells, and preventing HIV from spreading to other uninfected cells. Microbicides typically are administered via a gel, foam, or cream intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. In February 2009, NIH-supported researchers found that an investigational vaginal gel called PRO 2000, intended to prevent HIV infection in women, is safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). While additional data are needed to determine if PRO 2000 protects women from HIV infection, it was the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

- For more information, see [http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm](http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*

**Veterans With HIV and Alcohol Problems:** The Veteran's Aging Cohort Study (VACS), a cooperative agreement between NIH and the Department of Veterans Affairs, focuses on HIV-infected
veterans with alcohol use disorders. Alcohol abuse and dependence occur in approximately 25 percent of veterans. This work informs the design of interventions to modify the risk of alcohol- and liver-related mortality associated with HIV. The VACS index, which predicts health outcomes including HIV disease progression, was developed and is being evaluated as a clinically informative index for this study. Alcohol measures that can be used readily in HIV clinical settings have been validated and will guide the intensity of the alcohol intervention. Determining the presence of other health comorbidities and the level of antiretroviral adherence will help prioritize clinical care. Collaborations between VACS and other large studies will determine the generalizability of studies with veterans to other populations and inform use of electronic medical records from clinical samples with complex diseases for scientific research. This study also has evaluated the associations of "non-HIV" conditions (e.g. HCV, cardiovascular health) with alcohol, HIV, HIV treatment, and aging, and contributed data to all three international cross cohort collaborations—North American AIDS Cohort Collaboration on Research and Design (NA- ACCORD), ART Cohort Collaboration (ART-CC), and HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data (HIV CAUSAL)—addressing the question of when to start antiretroviral therapy. Progress of the VACS Study includes: enrollment of 7,015 patients, launch of a fourth follow-up survey (February 2008), and completion of blood and DNA collection and the initiated dissemination of tissue samples to researchers across the country. VACS also participates in collaborative grants, including those from the Veterans Affairs Health Services Research and Development Service, NIH, and the Medical Research Council UK.

- For more information, see [http://www.vacohort.org](http://www.vacohort.org)
- For more information, see [http://statepiaps.jhsph.edu/naaccord/](http://statepiaps.jhsph.edu/naaccord/)
- For more information, see [http://www.epi.bris.ac.uk/art-cohort/index.htm](http://www.epi.bris.ac.uk/art-cohort/index.htm)
- For more information, see [http://www.hsph.harvard.edu/faculty/miguel-hernan/hiv-causal](http://www.hsph.harvard.edu/faculty/miguel-hernan/hiv-causal)
- (E) (NIAAA)

**BARI 2D Clinical Trial:** Cardiovascular disease (CVD) is the leading cause of diabetes-related deaths—about 65 percent of people with diabetes die of heart disease or stroke. Recognizing the importance of comparative effectiveness research, NIH in FY 2000 awarded support for the BARI 2D clinical trial to evaluate management strategies for patients with stable coronary artery disease and type 2 diabetes. Its goal was to determine whether mortality and CVD event rates could be reduced by early coronary revascularization and intensive medical therapy compared with intensive medical therapy alone, and by an initial strategy of insulin sensitization compared with provision of insulin to treat hyperglycemia. The trial found that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of CVD event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

- For more information, see [http://content.nejm.org/cgi/reprint/360/24/2503.pdf](http://content.nejm.org/cgi/reprint/360/24/2503.pdf)
- For more information, see [http://content.nejm.org/cgi/reprint/360/24/2570.pdf](http://content.nejm.org/cgi/reprint/360/24/2570.pdf)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI, NIDDK)

**Action to Control Cardiovascular Risk in Diabetes (ACCORD):** ACCORD is a multicenter randomized clinical trial of 10,251 persons with type 2 diabetes who are at high risk of a cardiovascular disease (CVD) event. It was designed to assess whether the rate of major CVD events could be reduced by intensive control of blood sugar (glycemia) compared with the current standard of care,
intensive control of blood pressure compared with the current standard of care, or treatment of blood lipids with fibrate plus statins compared with treatment with statins alone. On February 6, 2008, NIH announced that participants receiving intensive glycemia treatment would be transitioned to the ACCORD standard treatment approach because higher mortality was observed among them. The glycemia main results were published in the *New England Journal of Medicine* in June 2008. They have substantial implications for the clinical treatment of diabetes, especially in older patients at high risk of CVD. The blood pressure and lipid trials are continuing as designed, with the last patient visits completed in June 2009.

- For more information, see [http://clinicaltrials.gov/ct2/show/](http://clinicaltrials.gov/ct2/show/)
- For more information, see [http://www.accordtrial.org](http://www.accordtrial.org)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI, CDC, NEI, NIA, NIDDK)

**Diabetes Prevention Program Outcomes Study (DPPOS) and Translational Research:** The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. This finding was true across all participating ethnic groups and for both men and women. The DPPOS is a long-term follow-up study of the DPP participants that is determining the durability of the interventions in preventing or delaying type 2 diabetes, and how the interventions affect the development of cardiovascular disease and other complications of diabetes. The DPP group was highly diverse (45 percent from minority ethnic and racial groups), and DPPOS will compare outcomes for women and men, and by age and ethnicity. Renewed in FY 2009 for a second 5-year phase, the DPPOS will enable researchers to better determine the lasting benefits of the interventions to diabetes prevention and/or the delay of onset. In addition, NIH is pursuing translational research efforts to develop more cost-effective methods of achieving the lifestyle change that delayed or prevented diabetes in the DPP, and better methods to identify those with prediabetes. For example, one translational effort is using the YMCA to deliver a DPP lifestyle intervention; data from a recent pilot study suggest that using the YMCA may be a low-cost way to deliver a lifestyle intervention to large numbers of people in the United States. Many of these translational research studies focus on minority populations disproportionately burdened by type 2 diabetes and by obesity, a significant risk factor for type 2 diabetes.

- For more information, see [http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc](http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDDK, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

**Framework for Adherence Research: A Workshop:** NIH organized and led an internal Adherence Research Network. The Network developed a formal evaluation plan for NIH's adherence research portfolio. As a part of the evaluation, NIH convened a think-tank style workshop, titled Framework for Adherence Research and Translation: A Blueprint for the Next Ten Years. The workshop was held March 9, 2008, in conjunction with the Third International Conference on HIV Treatment Adherence. The workshop participants discussed opportunities for future research on adherence as well as challenges to the field, including key methodological barriers that require a
renewed public health effort to improve adherence to preventive and treatment regimens.

- For more information, see http://obssr.od.nih.gov/scientific_areas/health_behaviour/adherence/index.aspx
- (O) (OBSSR, NIMH)

**Science of Dissemination and Implementation:** More present than ever within the research community is the belief that to optimize public health we must not only understand how to create the best interventions, but how to best ensure that they are delivered effectively within clinical and community practice. This is the focus of dissemination and implementation research, and building this knowledge base is imperative to get the best return on decades of investment in biomedical, behavioral, and social sciences research. The goal of the January 28-29, 2009, NIH-sponsored conference on the Science of Dissemination and Implementation was to provide a venue for the research community to exchange ideas, explore contemporary topics, and identify concepts, methods, and strategies to build research and organizational capacity for dissemination and implementation science. The conference was intended to complement the program announcement, Dissemination and Implementation Research in Health, which supports innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation, implementation, and maintenance of evidence-based practices by health providers, insurers, policy makers, and the public, and is a follow-up to an earlier conference, Building the Science of Dissemination and Implementation in the Service of Public Health.

- For more information, see http://obssr.od.nih.gov/funding_opportunities/foas/index.aspx
- For more information, see http://obssr.od.nih.gov/news_and_events/conferences_and_workshops/DI2009/index.html
- (E) (OBSSR, FIC, NCI, NHLBI, NIDA, NIDCD, NIDCR, NIMH, NINR, ODP/ODS)

**Oversight of Genetic Technologies:** In its April 2008 report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) identified gaps in the oversight of genetic testing and critical steps that should be taken to address them. The five key gaps in existing policy were: (1) regulations governing clinical laboratory quality; (2) oversight of the clinical validity of genetic tests; (3) transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) the ability of health professionals, the public health community, patients, and consumers to use these new tests effectively. Most immediately, SACGHS recommended the creation of a national registry of laboratory-developed tests that also would contain information about the tests’ complexity and clinical validity and utility.

- For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_004
- (O) (OSP/OBA, ATSDR)

**Research Training for Clinicians in Practice-Based Research Networks Yields Results:** When NIH awarded 6 7-year grants to establish 3 dental practice-based research networks (PBRNs), its aim was to assemble teams of practicing dentists to investigate with greater scientific rigor “everyday” issues in the delivery of oral health care. The impetus behind the networks was the frequent lack of research data to guide treatment decisions in the dentist's office. One of the key objectives to accomplishing the goal is providing the participating clinicians, many of whom have had no previous research experience, with the training and education needed to conduct clinical research effectively. The PBRNs have developed multiple methods of delivering research training to practicing clinicians,
including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. The real proof of the value of research training, of course, is whether research relevant to clinical practice is occurring—yes it is. Over the course of the grant period, the networks each will complete approximately 15 to 20 short studies. In early 2009 almost 90 study concepts had been approved, more than 20 were underway, and several had been completed and reported. The citations below are limited to those that deal with research training.

- For more information, see [http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm](http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm)
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems
- (E) [NIDCR]

**Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases:** The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its "Control Your Diabetes. For Life" educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

- For more information, see [http://www2.niddk.nih.gov/HealthEducation/](http://www2.niddk.nih.gov/HealthEducation/)
- For more information, see [http://ndep.nih.gov/](http://ndep.nih.gov/)
- For more information, see [http://nkdep.nih.gov/](http://nkdep.nih.gov/)
- For more information, see [http://win.niddk.nih.gov/](http://win.niddk.nih.gov/)
- This example also appears in Chapter 2: Minority Health and Health Disparities and Chapter 3: Health Communication and Information Campaigns and Clearinghouses
- (E) [NIDDK, CDC]

**Getting Proven Treatments into the Criminal Justice System:** Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical
need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

- For more information, see [http://www.cjdats.org/](http://www.cjdats.org/)
- For more information, see [http://www.drugabuse.gov/Blending/](http://www.drugabuse.gov/Blending/)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDA) (GPRA)

**Understanding and Promoting Health Literacy:** Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, where 43 percent of adults demonstrate only the most basic or below-basic levels of prose literacy. Low health literacy results in patients' inadequate engagement in decisions regarding their health care and can hinder their ability to realize the benefits of health care advances. Research has linked low or limited health literacy with such adverse outcomes as poorer self-management of chronic diseases, fewer healthy behaviors, higher rates of hospitalizations, and overall poorer health outcomes. An NIH program announcement supports research that increases our understanding of the health literacy problem and its relationship to health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy. In December 2008, a grantee meeting was convened to provide a venue for NIH-funded scientists conducting health literacy research to discuss lessons learned about health literacy-related topics, including measurement and methodology, actionable research (e.g., plain language, dissemination), and special populations (e.g., cognition, culture, and socioeconomic status). NIH is planning a fall workshop to highlight the state-of-the-science and to inform directions for reissuing the funding opportunity announcement in 2010.

- For more information, see [http://obssr.od.nih.gov/scientific_areas/social_culture_factors_in_health/health_literacy/index.asp](http://obssr.od.nih.gov/scientific_areas/social_culture_factors_in_health/health_literacy/index.asp)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

**Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care:** The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems.
CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

- For more information, see [http://crn.cancer.gov](http://crn.cancer.gov)
- For more information, see [http://breastscreening.cancer.gov/](http://breastscreening.cancer.gov/)
- This example also appears in Chapter 2: Cancer, Chapter 3: Epidemiological and Longitudinal Studies and Chapter 3: Disease Registries, Databases, and Biomedical Information Systems
- (I) (NCI)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

- For more information, see [http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm](http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm)
- This example also appears in Chapter 3: Molecular Biology and Basic Research and Chapter 3: Technology Development
- (E) (NIA)

Genomic Medicine: One of the promises of the Human Genome Project is the personalization of medicine. The time rapidly is approaching when health care providers will be able to use information
about each person's unique genetic makeup to develop individualized strategies for detecting, treating, and, ultimately, preventing disease. A number of initiatives are underway to explore this area, including the Multiplex Initiative, the Surgeon General's Family History Initiative, and the ClinSeq project. The Multiplex Initiative, a collaboration between NIH researchers, the Group Health Cooperative in Seattle, and the Henry Ford Health System in Detroit, studied the interest levels of healthy young adults in receiving genetic testing for eight common conditions. The purpose was to understand better how patients respond to the results of genetic tests. The U.S Surgeon General's Family History online tool, created through a collaborative effort involving the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Health Resources and Services Administration, allows people to record health conditions that have affected their relatives. The tool uses a three-generation pedigree to organize family health information in a format that people can easily share with their health care providers and other family members. Such information can lead to more proactive strategies for preventing disease and improving health. Finally, NIH researchers and their collaborators are enrolling volunteers in the ClinSeq project, which is piloting large-scale medical sequencing in a clinical setting, with a focus on cardiovascular disease.

- For more information, see [http://www.multiplex.nih.gov](http://www.multiplex.nih.gov)
- For more information, see [http://www.genome.gov/25521052](http://www.genome.gov/25521052)
- For more information, see [http://www.hhs.gov/familyhistory](http://www.hhs.gov/familyhistory)
- For more information, see [https://familyhistory.hhs.gov](https://familyhistory.hhs.gov)
- For more information, see [http://www.genome.gov/20519355](http://www.genome.gov/20519355)
- This example also appears in Chapter 3: *Genomics*
Collaboration, Education, and Genetic Test Translation Program for Rare Diseases (CETT): This research and education project was developed to make available genetic tests to patients from CLIA-certified laboratories. The vast majority of the known rare diseases are genetic disorders, thus genetic testing can be an essential part of the diagnosis and treatment continuum for rare diseases. The CETT program is a pilot program to translate new genetic tests from research in gene discovery to clinical practice and to meet an unfulfilled need for many rare diseases for which research did not translate to the development of a clinical diagnostic test. The mission of ORDR includes promoting the diagnosis of rare diseases and facilitating education in rare diseases. The CETT program encourages clinical laboratory and research collaborations, and supports the electronic collection of genetic and clinical data in public databases to leverage the information into new research and new treatments. During this pilot, the CETT program has supported the development of 34 genetic tests representing 67 diseases and 89 genes. The CETT Program also has piloted the development of educational materials about new test development for families and clinicians through the collaboration with advocacy and clinician experts in rare diseases and now is piloting the collection of de-identified clinical and genetic mutation information to be accessible publicly for the clinical and research community through partnership with NIH's National Center for Biotechnology Information. Tests put into development include DNM2 Centronuclear Myopathy, ROR2 Robinow Syndrome, ASPM, CDK5RAP2, CENPOJ, and MCPH1 for Autosomal Recessive Primary Microcephaly (University of Chicago); and ATP1A3 Rapid-Onset Dystonia Parkinsonism (Neurogenetics DNA Diagnostic Lab in Boston). Other tests put into development earlier include Urea Cycle Disorders (Baylor College of Medicine); Inclusion Body Myopathy Associated with Paget Disease and/or Frontotemporal Dementia (University of California at Irvine); and Duchenne Muscular Dystrophy and Becker Muscular Dystrophy (Emory University).

For more information, see [http://rarediseases.info.nih.gov/cettprogram/default.aspx](http://rarediseases.info.nih.gov/cettprogram/default.aspx)

Translating CAM Research Results into Clinical Practice: Results from a National Survey of Physicians and CAM Providers: In an initial investigation of the potential for information from complementary and alternative medicine (CAM) research to influence clinical practice, a 2007 national survey asked acupuncturists, naturopaths, internists, and rheumatologists about their awareness of CAM clinical trials, their ability to interpret research results, and their use of research evidence in decisionmaking. The survey focused on awareness of two major NIH-funded clinical trials that studied acupuncture or glucosamine/chondroitin for osteoarthritis of the knee. According to the survey, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both trials. A majority of respondents said they were "moderately confident" in their ability to interpret research literature; few—20 percent of acupuncturists, 25 percent of naturopaths, 17 percent of internists, and 33 percent of rheumatologists—said they were "very confident." All groups regarded clinical experience as "very important" in their decisionmaking, although CAM providers were more likely to rate it "most important." CAM providers were much more likely than physicians to rank research results as "least important," whereas physicians were much more likely to rate patient preferences as least important. The results of the survey demonstrate that CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice. Concerted efforts are recommended to better train all clinicians in interpretation and
use of evidence from research studies, and to improve the dissemination of research results.

- For more information, see [http://nccam.nih.gov/research/results/spotlight/041309.htm](http://nccam.nih.gov/research/results/spotlight/041309.htm)
- (E) (NCCAM)

**A Behavioral Intervention to Improve Obstetrical Care:** Background: Implementation of evidence-based obstetrical practices remains a significant challenge. Effective strategies to disseminate and implement such practices are needed. Adopting new evidence-based clinical practices and adapting them to different countries requires careful planning and adjustment of existing models to local conditions. Use of evidence-based guidelines improves quality of care, the behavior of health care practitioners, and the health outcomes of patients. Advance: This research focused on evaluating an intervention to facilitate the adoption of evidence-based practices in Latin American maternity hospitals. Using a cluster-randomized controlled trial design, this research evaluated the behavior and attitudes of birth attendants with respect to two evidence-based recommendations for obstetrical practice: the selective use of episiotomy and active management of the third stage of labor. The intervention was associated with an increase in use of prophylactic oxytocin and a decrease in the use of episiotomy. The intervention also was associated with reductions in the rate of postpartum hemorrhage. Birth attendants' readiness to change also increased in the hospitals receiving the intervention. The effects on the use of episiotomy and prophylactic oxytocin were sustained 12 months after the end of the intervention. Significance: This study, supported by NIH's International Clinical Operational and Health Services Research Training Award, addresses an implementation barrier and highlights that the use of evidence-based guidelines can improve the quality of care and the behavior of health care practitioners.

- For more information, see [http://content.nejm.org/cgi/content/abstract/358/18/1929](http://content.nejm.org/cgi/content/abstract/358/18/1929)
- For more information, see [http://www.fic.nih.gov/programs/training_grants/icohrta/](http://www.fic.nih.gov/programs/training_grants/icohrta/)
- (E) (FIC)

**The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain:** Before SPORT, many people who had chronic low back pain were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, while others feared that delaying surgery might cause even more damage. In the past 4 years, SPORT demonstrated that, indeed, surgery is superior to nonoperative treatments for the 3 most common causes of severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). However, people who have one of these conditions are not subjecting themselves to further harm if they adopt a "wait-and-see" approach before committing to surgery. The benefits of surgery to correct spinal stenosis, for example, were apparent as early as 6 weeks after surgery. Those patients who had severe slippage and discomfort due to lumbar spinal stenosis with degenerative spondylolisthesis seemed to benefit the most. Although people who did not have surgery reported some improvement 2 years into the study, those who had surgery seemed to be doing considerably better. Additionally, SPORT showed that combining two surgical procedures—decompressive laminectomy and fusion—did not help patients who had lumbar spinal stenosis without degenerative spondylolisthesis any more than decompressive laminectomy alone did. The findings regarding intervertebral disk herniation equally were meaningful. Two years after surgery, patients who had surgery for a herniated upper lumbar disk felt significantly better than those who had a lower disk repaired. Although more costly than nonoperative approaches, such as medications and physical therapy, lumbar diskectomy is a cost-effective treatment, regardless of whether the damaged disk is in
Bolstering the Research Continuum

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided $1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

ARRA-Funding Expands Research Capabilities: NCRR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCRR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCRR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCRR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCRR centers and Center-like programs. To
further advance the scientific progress of NCRR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA consortium strategic goals, enhance NCRR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCRR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCRR 2009-2013 Strategic Plan.

- For more information, see http://www.ncrr.nih.gov/recovery
- For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
- This example also appears in Chapter 2: Minority Health and Health Disparities and Chapter 3: Technology Development
- (E) (NCRR) (ARRA)

**Shared Instrumentation Grant and High-End Instrumentation Programs:** The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for $30,623,406; the HEI funded a total of 20 awards for $33,309,434. In FY 2009, NIH received $300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is $600,000 to $8 million.

- For more information, see http://www.ncrr.nih.gov/btinstruments
- For more information, see http://www.ncrr.nih.gov/recovery
- This example also appears in Chapter 3: Molecular Biology and Basic Research and Chapter 3: Technology Development
- (E) (NCRR) (ARRA)

**Using Systems Science Methodologies to Protect and Improve Population Health:** Solutions to complex problems, such as chronic disease, require approaches that can address a broad range of factors within a single framework—from genetic to environmental, cellular to behavioral, and biological to social. In May 2007, NIH sponsored a conference, Complex Approaches to Population Health, at the University of Michigan. This well-attended (300 persons) conference brought computational/mathematical modelers together with behavioral and social scientists to discuss longstanding problems in health that might be addressed with these modeling methods. A primary purpose of the conference was to raise awareness of systems science methodologies as a means for addressing population health problems. Informed by the 2007 meeting, NIH issued the initiative PAR-08-224, Using Systems Science Methodologies to Protect and Improve Population Health, in August
2008. The initiative solicits R21 grant applications that propose using systems science methodologies to address policy resistant health problems. There are three application receipt dates per year through 2011.

- (E) (OBSSR, FIC, NCCAM, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIEHS, NIMH, ODP, ODP/ODS)

**Blueprint Interdisciplinary Research Training:** Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

- For more information, see [http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm](http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm)
- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 3: Research Training and Career Development
- (E) (NIH Blueprint, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

**Recruiting for HIV Research Using Mobile Vaccine Units:** Evaluating the safety of candidate vaccines and treatments in humans depends on trust and partnership among scientists, clinicians, and study volunteers. NIH is reaching out to District of Columbia (DC)-area communities to raise awareness among diverse groups about HIV/AIDS. The mobile clinic is an extension of the vaccine clinic of the NIH Vaccine Research Center (VRC). The mobile clinic facilitates collaboration among scientists, clinicians, and study volunteers by raising awareness about HIV vaccines and by improving access for volunteers. With its new mobile clinic, the VRC enhances this vital collaboration by improving access for people in the DC metropolitan area who volunteer for clinical research studies to help find vaccines for HIV/AIDS and other infectious diseases. The mobile clinic can expand NIH outreach and recruitment efforts to neighborhoods in Baltimore and Frederick, Maryland, as well as DC and its suburban neighbors. The unit made its first community appearance in June 15, 2008, at the 33rd annual Capital Pride Festival (a signature event held by the lesbian/gay/bisexual/transgender community).

Stimulating Transformative Research in HIV/AIDS: In recent years, widespread public education campaigns in the United States have fueled progress in reducing HIV/AIDS transmission that occurs through the sharing of injection equipment among drug users. However, transmission through high-risk sexual contact is on the rise—these behaviors often are exacerbated by substance abuse and ensuing altered judgment. To achieve a more comprehensive approach to this problem, NIH initiated its Avant-Garde Award series in 2008, with the goal of stimulating high-impact research from varied scientific disciplines to pave new avenues of treatment for HIV disease and prevention of new HIV infections among drug abusers. This award, modeled after NIH's Pioneer Award, provides funds of up $0.5 million per year for 5 years and uses interviews with prospective candidates to more fully discern the scientist's and project's potential. One exemplary awardee is evaluating the effectiveness of expanding highly active antiretroviral treatment (HAART) coverage among injection drug users as a population-level HIV prevention strategy. A second is focusing on the ability of HIV to hijack key proteins involved in the regulation of host cell gene expression. A second initiative, the AIDS-Science Track Award for Research Transition (A-START), facilitates the entry of newly independent and early career investigators into the area of drug abuse and HIV/AIDS, an identified area of research need. Examples of projects supported through this mechanism include research on: (1) statistical models to explain ethnic disparities in HIV/AIDS among drug users, and (2) effects of morphine on immune responses to a candidate HIV vaccine in a primate model.

For more information, see [http://www.cdc.gov/hiv/topics/surveillance/incidence.htm](http://www.cdc.gov/hiv/topics/surveillance/incidence.htm)
For more information, see [http://www.drugabuse.gov/about/organization/arp](http://www.drugabuse.gov/about/organization/arp)
This example also appears in Chapter 2: *Infectious Diseases and Biodefense* (NIAID)

Institutional Development Award (IDeA) Program: The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico with historically low NIH funding. The IDeA program supports multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with the Lariat Networking Project, a pilot program that has enabled connectivity in six IDeA states in the Northwest (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming) in partnership with the University of Washington and the University of California, San Diego. The Louisiana Optical Network Initiative (LONI) followed, supporting high bandwidth connectivity in Louisiana and Mississippi. Recently, five IDeA states have formed the North East Cyberinfrastructure Consortium (Delaware, Maine, New Hampshire, Rhode Island, and Vermont). IDeANet ultimately will enable all institutions in the IDeA program to engage in national and international collaborations.

For more information, see [http://www.ncrr.nih.gov/riidea](http://www.ncrr.nih.gov/riidea)
This example also appears in Chapter 2: *Minority Health and Health Disparities* (NCRR) (GPRA)
Research Centers in Minority Institutions (RCMI): The RCMI program has developed and enhanced the research infrastructure of minority-serving institutions by expanding human and physical resources for conducting basic, clinical, and translational research. It began in 1985 in response to congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985; July 26, 1984; pages 78-79), directing funds to "establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health." The RCMI program has provided resources to acquire advanced instrumentation, renovate laboratory facilities, and improve research infrastructure. Additionally, it has enhanced faculty development, funded pilot projects, and supported core facilities. Because many RCMI investigators study diseases that disproportionately affect minorities, NIH support has brought more minority scientists into mainstream research and enhanced biomedical research focused on improving the health of racial and ethnic minorities and other medically underserved populations. The RCMI program includes various types of awards to help improve research capacity and reduce health disparities. For example, the RCMI Translational Research Network has fostered collaboration among researchers, developed and shared practices in disease prevention in local communities, and funded informatics tools for managing clinical research data. The RCMI program also has supported Clinical Research Education and Career Development awards that provide didactic training and mentor clinical research experiences to develop independent researchers.

- For more information, see http://www.ncrr.nih.gov/rircmi
- For more information, see http://www.ncrr.nih.gov/rtrn
- For more information, see http://www.ncrr.nih.gov/crecd
- This example also appears in Chapter 2: Minority Health and Health Disparities
- (E) (NCRR, NCMHD, NHLBI, NIA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Research Training and Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, National Need and Priorities for Veterinarians in Biomedical Research and Critical Needs for Research in Veterinary Science, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides research training awards ("T" Awards) in biomedical research specifically for veterinarians and veterinary students. During FY 2008, more than 75 veterinarians received research training under the "T" mechanism. The mentored Career Development Awards ("K" Awards) to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2008, 22 career development "K" awards were made to young veterinary investigators to increase the number of biomedical researchers with this expertise. Additionally, another initiative encourages the training of veterinarians in nonhuman primate clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

- For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
- This example also appears in Chapter 3: Research Training and Career Development
- (E) (NCRR)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of
disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatistical and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

- For more information, see [http://www.nhlbi.nih.gov/resources/chi/index.htm](http://www.nhlbi.nih.gov/resources/chi/index.htm)
- This example also appears in Chapter 2: Autoimmune Diseases and Chapter 3: Technology Development
- (I) (NIAMS, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

**Translational Research at the Aging/Cancer Interface:** The NIH Translational Research at the Aging/Cancer Interface initiative was established in 2008 to enhance research in the overlapping areas of human aging and cancer by (1) integrating knowledge of basic processes in cancer biology and aging into clinical care of older patients with cancer ("bench to bedside"), and (2) exploring clinical observations from the patient care setting at more basic and molecular levels ("bedside to bench"). Research supported by this initiative holds potential for improving prevention, diagnosis, and disease management; improving the health and well-being of older adults at risk for or diagnosed with cancer; and decreasing the functional impairment and morbidity associated with cancer in this population.

- For more information, see [http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html](http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html)
- This example also appears in Chapter 2: Cancer
- (E) (NIA)

**Public Trust Initiative:** The NIH Public Trust Initiative (PTI), in partnership with the NIH Roadmap for Research, seeks to provide an inventory of activities that NIH and its individual Institutes and Centers are engaged in that involve public constituents, and that are intended to inform, educate, hear from, and serve the public. In 2008, NIH extended a new opportunity in community-based research under the PTI, the Partners in Research initiative (PIR). The PIR provides a unique opportunity for scientists to team up with community organizations to address the practical questions surrounding the development of true partnerships between researchers and the public. The goals of these partnerships are to: facilitate discussion of the health care needs and interests of the community; develop and implement research programs that address these needs; study methods to engage and inform the public regarding health science; improve public understanding of the benefits of publicly funded research; and communicate the results of this research. NIH received more than 200 applications in response to this opportunity, and a total of 37 projects were funded in 2008. On October 26-27, 2009, NIH convened a PIR workshop to examine the experiences of those participating in the PIR program. Participants discussed various aspects of the PIR program, including, for example, building partnerships, establishing criteria for a good partnership, and identifying challenges to this type of research.

- For more information, see [http://publictrust.nih.gov](http://publictrust.nih.gov)
Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases: NIH is working to develop new approaches to treating serious, chronic, genetic diseases like cystic fibrosis and mucopolysaccharidosis. For example, the Gene Therapy and Cystic Fibrosis Centers Program currently supports Molecular Therapy Centers and a Cystic Fibrosis Research and Translation Core Center. Molecular Therapy Centers provide shared resources to a group of investigators to facilitate development of molecular therapies for the treatment of cystic fibrosis and other genetic metabolic diseases, like so-called lysosomal storage disorders such as mucopolysaccharidosis I. The Cystic Fibrosis Research and Translation Core Center provides resources and supports research on many aspects of the pathogenesis and treatment of cystic fibrosis. These centers have made important strides in recent years, including the study of promising candidate therapeutics. One of these, PTC124, is designed to overcome a mutation in the cystic fibrosis gene that otherwise yields a truncated, inactive cystic fibrosis protein. Other centers are screening libraries of compounds for other agents that might be safe and effective therapeutics for cystic fibrosis and other metabolic diseases.

  PMCID: PMC2538881.
- For more information, see http://www2.niddk.nih.gov/Research/ScientificAreas/GeneticGeneTherapy/GCTR.htm
- This example also appears in Chapter 2: Chronic Diseases and Organ Systems

Training Activities of the Clinical and Translational Science Award Program: Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip members of clinical research teams with the special training and experience they need to succeed. NIH expanded its clinical research training programs through Roadmap T32 and K12 programs that largely have been assimilated into Clinical and Translational Science Awards (CTSAs). Clinical research trainees learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to compete successfully for funding in a mentored environment. The CTSA training program already is providing more than 1,000 research training and career development opportunities in multiple individual disciplines. As mandated in Section 106 of the National Institutes of Health Reform Act of 2006 (Pub. L. No. 109-482), NIH will evaluate the outcomes and effectiveness of the CTSA training programs. The evaluation will include surveys of trainees, scholars, and mentors and will address pediatric clinical research training issues. In addition, the evaluation will conduct secondary analyses of pediatric clinical research training data collected by the CTSA program. This is part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA recipient also evaluates his or her own training activities, and the CTSA Education/Career Development Key Function Committee provides a forum in which best educational practices can be identified. The CTSA program was initiated in September 2006, so the long-term impact of the CTSA program will not be known for 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years. For example, the CTSA consortium defined training standards for core competencies in clinical and translational research. The consortium identified the skills, attitudes, and knowledge that investigators need to participate successfully in multidisciplinary teams of clinician-scientists.
Interdisciplinary Research Consortia Funded by the NIH Roadmap: One of the four main initiatives established by the NIH Roadmap's Interdisciplinary Research Work Group was a grant program to fund large-scale consortia to support interdisciplinary research. In total, NIH funded nine collaborative teams located across the United States. Each focuses on a particular health problem or process, including substance abuse and stress; obesity; developmental disorders; the process of aging; providing fertility options for cancer survivors; engineering healthy tissue to treat diabetes, heart disease and oral/craniofacial disorders; psychiatric disorders; drug/medications development; and genome engineering. The initial results suggest ways in which this team science approach helps to increase cooperation within and between academic institutions, as well as advancing the individual missions of NIH ICs.

Enhancing Behavioral and Social Sciences in Medical Education: In 2004, the Institute of Medicine (IOM) released its report on Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula, which NIH funded. The report summarized how medical school curricula should be enhanced to address critical health issues faced in the United States today. One major finding was that approximately half of all causes of mortality in the United States are linked to social and behavioral factors such as smoking, diet, alcohol, sedentary lifestyle, and accidents. While generally it is recognized that biomedical research alone cannot address these issues, the IOM found that the curriculum in most U.S. medical schools does not provide sufficient teaching about these behavioral and social risk factors. In response to the IOM report, NIH issued a 2004 RFA and funded grants to nine medical schools to develop, pilot, and disseminate behavioral and social sciences modified curricula across the six domains identified by the IOM: (1) Mind-Body Interactions in Health and Disease, (2) Patient Behavior, (3) Physician Role and Behavior, (4) Physician-Patient Interactions, (5) Social and Cultural Issues in Health Care, and (6) Health Policy and Economics. Working in close collaboration, these medical schools are addressing how to incorporate behavioral and social sciences content throughout all 4 years of medical school in both the preclinical and clinical curricula. About 6,100 medical students will be affected by curricular innovations over the next 2 years of this 5-year collaborative effort.

Clinical and Translational Science Award (CTSA) Program: The CTSA program is a partnership between NIH and a national consortium of 46 academic health centers and research institutions to build academic homes for clinical and translational research. By 2011, NIH expects to
fund 60 CTSA institutions at a total cost of $500 million per year. The CTSA program is designed to translate more efficiently the rapidly evolving knowledge developed in basic biomedical research into treatments to improve human health. The CTSA institutions are designing clinical and research informatics tools, forging new partnerships with private and public health care organizations, expanding outreach to minority and medically underserved communities, and developing better designs for clinical trials. Additionally, the CTSAs are training the next generation of clinical and translational researchers to excel in interdisciplinary team science. Working together, the consortium is developing and disseminating best practices, policies, procedures, and other measures to advance collaborative clinical and translational research. At the same time, NIH is encouraging active collaboration among CTSAs and other NIH-funded programs and investigators to leverage program resources and increase efficiencies. The CTSA program is the primary initiative for addressing the NIH Roadmap for Medical Research theme to Re-Engineer the Clinical Research Enterprise.

- For more information, see [http://www.ncrr.nih.gov/ctsa](http://www.ncrr.nih.gov/ctsa)
- For more information, see [http://www.ctsaweb.org](http://www.ctsaweb.org)
- (E) (NCRR, Common Fund - all ICs participate)

**Clinical and Translational Science Award (CTSA) Program Evaluation:** NIH recognizes the importance of accountability and the need to evaluate and demonstrate progress toward meeting the ambitious goals of the CTSA program. For this reason, each CTSA grantee is required to conduct an institutional evaluation and to submit an annual status report to NIH. Institutional evaluators also participate in the CTSA consortium's Evaluation Key Function Committee, which provides an interactive forum to share and disseminate best practices and approaches to evaluating CTSA grantee programs. Additionally, NIH has hired external evaluators from Westat, a leading government services organization, to evaluate implementation of the CTSA program independently, to consider stakeholders' needs and perceptions, and to identify barriers to and facilitators of progress. As data are collected and as the program continues to mature, evaluation efforts will capture long-term outcomes and the impact the CTSA program has had on transforming the discipline of clinical and translational research. NIH will ensure that program findings and outcomes are disseminated to stakeholders, including researchers, advocacy groups, and Congress.

- For more information, see [http://www.ctsaweb.org](http://www.ctsaweb.org)
- (E) (NCRR, Common Fund - all ICs participate)

**Clinical and Translational Science Award (CTSA) Program Progress:** Launched in 2006, NIH has made significant progress in building a national consortium for clinical and translational research. Since 2008, 22 new CTSAs joined the consortium, adding representation from eight new states, additional pediatric expertise, and greater informatics capabilities. At the national level, the CTSA consortium has identified five strategic goals: developing strategies and resources to move laboratory discoveries into early clinical testing (T1 translation), reducing complexities and improving ways clinical and translational research is conducted, enhancing training and career development of clinical and translational investigators, encouraging consortium-wide collaborations, and improving the health of communities across the nation—with an emphasis on community engagement and comparative effectiveness research. Working together, the consortium has made substantial progress in improving the management of clinical research, developing core competencies in clinical and translational science, and accelerating the dissemination of research findings into clinical practice. The momentum of the CTSA consortium continues to build as new connections are emerging rapidly within,
across, and beyond the consortium. For example, CTSAs are connecting with the following NIH-funded institutions: Emory University (Atlanta, Georgia) is partnering with Morehouse School of Medicine; Vanderbilt University (Nashville, Tennessee) is partnering with Meharry Medical College; and Weill Cornell Medical College (New York, New York) is partnering with Hunter College.

For more information, see http://www.ncrr.nih.gov
For more information, see http://www.ctsaweb.org
For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009
This example also appears in Chapter 2: Minority Health and Health Disparities
(E) (NCRR, Common Fund - all ICs participate)

Collaborative Community-Based Research: NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority and other medically underserved communities where health disparities persist. Programs such as the Institutional Development Award (IDeA) are encouraging efforts to build and strengthen partnerships among government agencies, academic and private-sector organizations, community health providers, and organizations that also are working to improve community health outcomes. Translational, community-based research funded in several IDeA states, in both urban and rural settings, is focusing on:

- Enhancing recruitment and retention of research subjects through community buy-in
- Implementing practical and effective research protocols in community health care settings
- Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FYs 2008 and 2009, NIH conducted workshops to gather specific recommendations from the community that are helping to shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities. Workshop participants included other HHS-agencies such as AHRQ, CDC, the Indian Health Service, and HRSA.

For more information, see http://www.ncrr.nih.gov/research_infrastructure
This example also appears in Chapter 2: Minority Health and Health Disparities
(E) (NCRR)

Community-Based Participatory Research (CBPR): CBPR is an orientation to research that requires a collaborative approach to involve community stakeholders throughout all stages of research projects. This community input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. NIH issued three funding opportunity announcements (FOAs) on CBPR in January 2008. One FOA, Community Participation in Research, solicits jointly conducted intervention research. The remaining FOAs, Community Participation Research Targeting the Medically Underserved, solicit jointly conducted research in medically underserved areas/populations; all three FOAs focus on health promotion, disease prevention, and health disparities. A corresponding technical assistance workshop, Leap into the Community, convened February 2008 and offered comprehensive instruction from NIH program and review officials on the CBPR approach and preparing responsive applications to the FOAs. Outreach and training activities on CBPR have included the creation of an educational brochure (November 2007); organization of two special sessions at annual scientific meetings for the Society of Behavioral Medicine and the American Sociological Association on the principles and efficacy of CBPR and showcasing successful NIH-funded research projects (March 2008 and August 2009, respectively);
Community Participation in Health Disparities Intervention Research Program: NIH supports the development, implementation, and evaluation of intervention research by using community-based participatory research (CBPR) principles and methods in targeting diseases of major public health importance in health disparity communities. This unique multiyear CBPR initiative promotes participatory research collaborations between scientific researchers and their community partners and will engage communities in all stages of the research process for a total of 11 years (3-year planning phase, 5-year intervention phase, and 3-year dissemination phase). The participatory partnerships formed between researchers and the community are expected to (1) transform the research questions from researcher to community-centered; (2) focus the research area, strategies, and methods to address those diseases and conditions of highest community interest and need; and (3) accelerate the identification and testing of interventions that are likely to make the largest difference in the health of the community. The CBPR initiative began in FY 2005 with the award of 25 3-year research planning grants. CBPR planning grantees conducted needs assessments, focus groups, and pilot intervention studies for addressing health disparities among health disparity populations in 20 states. In FY 2008, 40 5-year intervention research grants focusing on diabetes, cancer, cardiovascular disease, substance abuse, and other diseases and conditions were awarded. This intervention phase will be followed by a competition for 3-year dissemination grants to be awarded in FY 2013. In May 2009, RFA MD-09-006, "Recovery Act Limited Competition: NCMHD Community Participation in Health Disparities Intervention Research Planning Phase," was issued for a 2-year planning research phase. Awards for this phase were made in FY 2009. Current CBPR pilot intervention research studies include:

- Suicide and alcohol use prevention among Alaska Native youth living in five communities in Alaska
- HIV/AIDS prevention among African Americans in North Carolina
- Obesity prevention using individual, family, and community-level interventions among Native Hawaiian and Pacific Islanders in Hawaii
- Diabetes prevention among Hispanic communities in border areas in Texas
- Hypertension prevention among Filipino Americans in New York City and New Jersey
- Cancer prevention among low-income Appalachian communities in Ohio by increasing colorectal cancer screening
Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogentially active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are
studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.


For more information, see [http://www.bcerc.org/](http://www.bcerc.org/)

This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*

### Cancer Health Disparities Research Programs and Initiatives:

NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMAP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities
and underserved populations with abnormal cancer screening results receive appropriate care.

- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

- For more information, see [http://crchd.cancer.gov/](http://crchd.cancer.gov/)
- For more information, see [http://crchd.cancer.gov/cnp/background.html](http://crchd.cancer.gov/cnp/background.html)
- For more information, see [http://crchd.cancer.gov/pnp/pnrp-index.html](http://crchd.cancer.gov/pnp/pnrp-index.html)
- For more information, see [http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html](http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html)
- This example also appears in Chapter 2: Cancer, Chapter 2: Minority Health and Health Disparities and Chapter 3: Molecular Biology and Basic Research

(C) (NCI)

**Collaborations Between Minority-Serving Institutions and Cancer Centers:** The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

- For more information, see [http://crchd.cancer.gov/research/miccp-overview.html](http://crchd.cancer.gov/research/miccp-overview.html)
- For more information, see [http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406](http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406)
- This example also appears in Chapter 2: Cancer, Chapter 2: Minority Health and Health Disparities and Chapter 3: Molecular Biology and Basic Research

(C) (NCI)

**Ethical, Legal, and Social Implications (ELSI) Centers of Excellence:** NHGRI's ELSI program has established a network of Centers of Excellence in ELSI Research. Currently, four full Centers and three exploratory Centers are bringing together investigators of diverse expertise to
investigate issues related to:

- Intellectual property of genetic information
- Translation of genetic information to health care
- Genetic research that involves human participants
- Use of genetic information and technologies in non-health care settings, such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on the concepts of race, ethnicity, and individual and/or group identity
- Implications of uncovering genomic contributions to human traits and behaviors, such as aging or addictions
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

For more information, see http://www.genome.gov/10001618
This example also appears in Chapter 3: Genomics
(E) (NHGRI)

Advancing Novel Science in Women's Health Research (ANSWHR): A trans-NIH grants program, ANSWHR, is encouraging innovative, interdisciplinary research that promotes new concepts in women's health research and the study of sex/gender differences. Grants have been funded in areas such as genetic pathways in systemic lupus erythematosus (Lupus), sex differences in stress, sex differences relating to the vulnerability to cocaine addiction, inflammation and insulin sensitivity in obese pregnant women, novel ovarian cancer detection agents, evaluation of diagnostic techniques for cardiovascular events, sex differences in HIV/AIDS antiretroviral treatment, and sex differences and cognitive function. Based on responses to this program, ANSWHR is becoming an important scientific program that is enabling both early-stage investigators and veteran researchers to test nascent scientific concepts.

For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html
For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html
(E) (ORWH, FIC, NCI, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, OBSSR, ODP/ODS)

Research Enhancement Awards Program (REAP): REAP increases the number of new research studies of women's health and/or the study of sex and gender factors by collaborating with the NIH ICs to identify and co-fund meritorious research grants that have just missed the cutoff for funding. Examples of scientific areas funded through this mechanism included breast reconstruction, estrogen effects on wasting of skeletal muscle, activin target genes in the regulation of ovarian follicle development, and improving contraceptive use and reducing unintended pregnancy rates among young low-income women.

For more information, see http://orwh.od.nih.gov/research/recap.html
(E) (ORWH, NCCAM, NCI, NIAMS, NICHD, NIDCR, NINDS)

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:
• The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
• The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
• The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.
• The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
• The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
• The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
• The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp
- This example also appears in Chapter 2: Autoimmune Diseases and Chapter 2: Minority Health and Health Disparities
- (E) (NIAMS)

Improving Research Efficiency

2009 Institute of Medicine Report, The U.S. Commitment to Global Health:
Recommendations for the Public and Private Sectors: The recently released IOM report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors, reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, America’s Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled The U.S. Commitment to Global Health: Recommendations for the New Administration, was released in December 2008. In May 2009, the final report, titled The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors, was released.
Harmonization of Adverse Event Reporting, Analysis, and Communication: Clinical Research Policy Analysis and Harmonization (CRpac) has led a major effort to improve understanding and compliance with adverse event reporting requirements and to standardize the reporting of adverse event data. An interagency task force, the Federal Adverse Event Task Force (FAET), has been conducting a comprehensive assessment and analysis of existing Federal policies to identify opportunities for greater harmonization in reporting, analyzing, and communicating adverse events in research. The task force, which includes NIH, FDA, OHRP, CDC, AHRQ, VA, and DOD, has developed a core adverse event report that investigators can send to multiple agencies and develop best practices for reporting, analysis, and application of safety information. In addition, FAET has developed a Basal Adverse Event Report (BAER) that provides a single baseline set of information for reporting adverse events and unanticipated problems that is acceptable to multiple Federal agencies. It includes data elements needed for adverse event and unanticipated event reporting across all types of clinical research including behavioral, social science, epidemiologic, and surveillance studies. As a next step, a Web-based portal is under development to provide a seamless online method to submit adverse event reports. The goal is to develop a user-friendly electronic submission system to report an adverse event to NIH, FDA, and other government agencies from investigators, sponsors, physicians, and the public.

- For more information, see [http://oba.od.nih.gov/policy/policy_issues.html#CRP_001](http://oba.od.nih.gov/policy/policy_issues.html#CRP_001)
- (O) [OSP/OBA, Common Fund - all ICs participate](http://oba.od.nih.gov/policy/policy_issues.html#CRP_001)