

Summary of Research Activities by Disease Category

Chronic Diseases and Organ Systems

When someone has a chronic disease, doctors may use a variety of tools—such as blood tests, X-rays, and more expensive or invasive technologies—to assess whether the disease is progressing or if the person is responding to treatment. The physical changes that these tests show, however, do not always correlate with patients' subjective experiences of symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability.

Measurement of subjective patient-reported outcomes is particularly important in clinical trials in which two treatments may be comparable in limiting or curing disease but have different effects on symptoms, functioning, or other aspects of patients' quality of life. Recognizing the importance of interventions that improve the day-to-day lives of people who have chronic diseases, NIH has created the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative to develop an analytic tool that researchers can use to assess systematically and objectively several factors that are meaningful to patients from different walks of life who have various chronic diseases.

Already, investigators have found that a short, 10-question survey, administered using the computer adaptive testing system of PROMIS, outperforms the most commonly used, paper-based, self-reporting assessment tool for arthritis disability. As the PROMIS initiative enters its second phase, researchers will further validate and evaluate PROMIS' usefulness in NIH-supported clinical trials; facilitate adoption of PROMIS by the clinical research community; and build partnerships to sustain PROMIS once the second phase of NIH support is complete. The ultimate goal is for PROMIS to fulfill its "promise" of reliably integrating into clinical testing those outcomes that have the greatest effects on patients' lives.

Introduction

Chronic diseases are defined by the U.S. Department of Health and Human Services as conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living. Chronic diseases place a considerable burden on the U.S. health care system, the national economy, and the health and lives of individual patients and their families. Not all chronic diseases are fatal, and not all fatal conditions are chronic. Nonetheless, 7 of every 10 Americans who die each year—more than 1.7 million people—succumb to a chronic disease.⁹⁷ Health-damaging behaviors such as drug use (e.g., tobacco, excessive alcohol, or other drug), lack of physical activity, and poor eating habits, contribute to many chronic diseases, whereas others may result from the long-term effect of early exposure to toxins or other environmental factors, especially in individuals with a higher genetic risk of disease. A shared aspect of many chronic diseases is chronic pain and other disease-associated disability that interferes with quality of life: approximately one-fourth of Americans living with a chronic illness—fully 1 in 10 Americans overall—experience significant limitations on daily activities due to their condition. As many as 75 million Americans suffer from 2 or more concurrent chronic conditions,⁹⁸ placing them at risk not only for worse overall health but also for significant financial burden, including higher prescription drug and total out-of-pocket health care spending. Many chronic diseases that are common in the United States—such as type 2 diabetes, obesity, and heart disease—also have a substantial impact on global morbidity and mortality.

Many of the most burdensome chronic diseases develop over time and become more prevalent with age (e.g., osteoarthritis, chronic kidney disease, vision loss); less commonly, chronic disease may manifest from birth as a result of one or more faulty genes (e.g., sickle cell anemia, hemophilia) or at

other times during childhood (e.g., allergies, asthma). Some chronic diseases are common in the U.S. population, as in the case of heart disease, which is the leading cause of death, while others are relatively rare, such as cystic fibrosis, which affects approximately 30,000 Americans. Certain chronic diseases represent growing public health issues, such as the increases in obesity and type 2 diabetes in children and adults.

Some chronic diseases and conditions may affect more than one organ. For example, diabetes can affect the pancreas, heart, kidneys, eyes, and nerve endings in the limbs. In addition, some chronic diseases, including addiction and other mental illnesses, have significant mental, psychological, and behavioral components. For these reasons, modern medicine requires an integrated understanding of the complex interactions among multiple organs, the nervous system, the circulatory system, the immune system, and the endocrine system. Thus, research to combat chronic illness involves significant trans-NIH collaboration in addition to the mission-specific work of each IC. NIH supports basic research on both normal and disease states of organ systems to understand the initiation and progression of chronic diseases, as well as translational and clinical research on new biomedical and behavioral strategies to prevent, preempt, diagnose, treat, and cure these diseases. The ultimate goal is to reduce or eliminate morbidity and mortality while improving quality of life for those living with these often debilitating conditions.

This section provides information about NIH's activities related to a number of major chronic diseases, as well as research on aspects of the function of various organ systems. Additional major chronic diseases are discussed in this chapter in the sections "Cancer" (cancers of all organs and tissues, including blood), "Neuroscience and Disorders of the Nervous System" (e.g., Parkinson's disease, Alzheimer's disease, autism, and epilepsy), "Autoimmune Diseases" (e.g., lupus, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease), and "Infectious Diseases and Biodefense" (e.g., HIV/AIDS and hepatitis). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, organ transplantation research and the related issue of establishing immune tolerance to transplanted organs are highlighted in this section. Research on complementary and alternative medicine (CAM) approaches to combating chronic disease also is discussed. NIH supports research to reduce the pain associated with long-term diseases and to find innovative and effective forms of palliative care to relieve disease symptoms. Some of these efforts are highlighted in this section; more information on NIH pain research also can be found at the NIH Pain Consortium website.

⁹⁷ Centers for Disease Control and Prevention. *Chronic Diseases: The Power to Prevent, the Call to Control*. Atlanta, GA, 2009. Available at: <http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm>.

⁹⁸ Hwang W, et al. *Health Affairs* 2001;(20)268-9.

Burden of Illness and Related Health Statistics

The prevalence and burden of chronic diseases are substantial. About 133 million Americans—nearly 1 in 2 adults—live with at least 1 chronic illness, and as noted above, each year 1.7 million people in the United States die from a chronic disease.⁹⁹ Chronic disease disables or limits activity for almost 12 percent of all adults, including more than one-third of adults ages 65 and older.¹⁰⁰ Notably, the percentage of U.S. children and adolescents with a chronic health condition has increased significantly, from 1.8 percent in the 1960s to more than 7 percent in 2004. Furthermore, the increasing prevalence of patients with 1 or multiple chronic diseases has a significant impact on health care delivery and the economy: More than 75 percent of health care costs are due to chronic conditions.¹⁰¹

Worldwide, the burden of chronic disease is increasing rapidly. By 2015, chronic diseases will be the most common cause of death even in the poorest countries. In 2005, chronic diseases contributed approximately 60 percent of the 58 million total deaths in the world and almost three-quarters of the

burden of disease (measured in disability-adjusted life-years) in those ages 30 or older.¹⁰²

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More detailed data on the U.S. burden of many of the major chronic illnesses are provided at the end of this section.

⁹⁹ *Chronic Diseases: The Power to Prevent The Call to Control.*

<http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm>

¹⁰⁰ National Center for Health Statistics. *Health, United States, 2008 with Chartbook*, Hyattsville, MD, 2009.

¹⁰¹ *Chronic Diseases: The Power to Prevent The Call to Control.*

<http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm>

¹⁰² Quam L, et al. *Lancet* 2006;368(9543):1221-3. PMID: 17027712.

NIH Funding for Chronic Diseases and Organ Systems Research

Currently, NIH does not collect the data necessary to provide an aggregate figure for expenditures on chronic diseases and organ systems research, although this capacity is expected to be developed in the future for integration with RCDC. The table at the end of this chapter provides funding estimates for many of the areas of research associated with chronic diseases and organ systems (see *Estimates of Funding for Various Research, Condition, and Disease Categories*). Because of overlap among the areas of research listed in the table, and because research on chronic disease and organ systems may account for only a portion of the funding for a given area, the figures in that table cannot be used to provide an aggregate number.

About Various Chronic Diseases and Conditions

Links to detailed information on many specific chronic health conditions can be found at <http://health.nih.gov>. Following are examples of chronic diseases and conditions addressed by NIH-funded research, with links to major associated research programs and NIH research fact sheets.

Cardiovascular Diseases: Heart disease is the leading cause of death in the United States.¹⁰³

Coronary heart disease, the most common type of [heart disease](#), occurs when plaque builds up in the arteries that supply blood to the heart muscle. Coronary heart disease can cause angina (chest pain) or a heart attack and, over time, contributes to serious disability or death. Other chronic, serious cardiovascular conditions include [hypertension](#), heart failure, atrial fibrillation, and peripheral arterial disease. Additional, and sometimes rare, cardiovascular disorders include Marfan syndrome, a connective tissue disorder that affects the heart and blood vessels and other parts of the body; long QT syndrome, a disorder of the heart's electrical activity that may cause a sudden, uncontrollable, and dangerous heart rhythm; and congenital heart defects.

Lung Diseases: [Chronic obstructive pulmonary disease](#), the fourth leading cause of death in the United States,¹⁰⁴ causes airflow obstruction in the lungs that makes breathing difficult. [Asthma](#), the most common chronic disease of childhood, is characterized by inflamed and narrowed airways. Rare lung diseases include [cystic fibrosis](#), an inherited disease that affects multiple organs, and idiopathic pulmonary fibrosis, in which lung tissue becomes thick and stiff, resulting in loss of function.¹⁰⁵

Diabetes Mellitus: Diabetes is characterized by abnormally high levels of glucose (sugar) in the

blood. It can be caused by either autoimmune destruction of cells in the pancreas ([type 1](#)) or the inability of tissues, such as the muscles and liver, to use insulin properly ([type 2](#)). Diabetes can result in complications such as heart disease, stroke, hypertension, and nerve damage. It also is the leading cause of kidney failure and nontraumatic lower limb amputation in the United States and of new cases of blindness among working-age Americans. Women with no prior history of diabetes who develop high blood sugar levels while pregnant are said to have [gestational diabetes mellitus](#) (GDM). GDM affects 3-8 percent of all pregnant women and can have long-term health consequences for both the fetus and the mother, including an increased risk of developing type 2 diabetes later in life.¹⁰⁶

[Obesity](#): Obesity, which has risen to epidemic levels in the United States, is a chronic, relapsing health problem caused by an interaction of genes, [environment](#), and behavior. A common measure of overweight and obesity in adults is body mass index (BMI)—a calculation based on height and weight. For most people, BMI correlates with their amount of body fat and serves as an indicator of weight-related health risks. An adult with a BMI between 25 and 29.9 is considered overweight, whereas an adult with a BMI of 30 or higher is considered obese. Although BMI numbers are interpreted differently for children, their rates of overweight and obesity have risen dramatically in recent years. Obesity increases the risk of other chronic conditions, including type 2 diabetes, heart disease, certain cancers, osteoarthritis, liver and gallbladder disease, urinary incontinence, and sleep apnea, and also is associated with depression.

[Kidney Diseases](#): [Chronic kidney disease](#) is the progressive, permanent loss of kidney function that can result from physical injury or from a disease that damages the kidney such as diabetes, high blood pressure, or polycystic kidney disease. Patients with advanced chronic kidney disease may progress to irreversible kidney failure and require immediate, life-saving dialysis or a kidney transplant. Chronic kidney disease is a growing problem in the United States.

[Digestive](#) and [Urologic Diseases](#): Diseases of the digestive system involve many organs (e.g., intestines, stomach, liver, gallbladder, and pancreas) and include disorders such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, celiac disease, peptic ulcer disease, gallstones, gastroesophageal reflux disease, and chronic pancreatitis. Illnesses of the genitourinary tract are similarly diverse and include chronic prostatitis, benign prostatic hyperplasia, interstitial cystitis and painful bladder syndrome, urinary incontinence, and urinary tract infections.

[Liver Diseases](#): Chronic forms of liver disease include chronic viral hepatitis (B and C), alcoholic and nonalcoholic fatty liver disease, genetic diseases such as hemochromatosis, and autoimmune diseases such as primary sclerosing cholangitis. Significant liver injury sometimes can result from adverse reactions to medical drugs and other compounds. Although many organ systems may be damaged by chronic alcohol use, alcoholic liver disease is the leading cause of death from excessive and long-term alcohol consumption.

[Blood Diseases](#): Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with [sickle cell diseases](#) and Cooley's anemia. Patients can experience pain, fatigue, and other serious health problems. Chronic inherited bleeding disorders, such as hemophilia and von Willebrand disease, leave patients at risk for uncontrollable bleeding.

[Musculoskeletal Disorders](#): [Osteoarthritis](#), the most common form of arthritis, is a degenerative disease caused by the breakdown of cartilage, leading to pain, swelling, and stiffness in joints. [Osteoporosis](#), another musculoskeletal disease that causes significant disability, occurs when bones become thin, weak, and fragile. Other chronic bone diseases include osteogenesis imperfecta, a genetic disease that causes bones to become brittle and break for no known reason, and Paget's disease of bone, in which bones grow larger and weaker than normal. Many older adults develop chronic low back pain as the bones in the spine change shape and the spinal

ligaments that hold the bones in place weaken. Soft tissue sprains and strains can begin as acute injuries but often cause chronic problems because the injured ligaments, tendons, or muscles never fully recover and are susceptible to re-injury.

Skin Disorders: Skin, the largest organ of the body, separates the internal organs from the outside environment, protects against bacteria and viruses, regulates body temperature, and provides sensory information about surroundings. The most common type of eczema—inflammation of the skin—is atopic dermatitis, which is characterized by dry, itchy skin.

Vision and **Hearing Loss:** The eyes and ears contain specialized nerve cells for sensing light and sound and for relaying these signals to the brain. Death or damage to light-detecting cells (e.g., retinopathy, retinitis pigmentosa) or to cells of the optic nerve (e.g., [glaucoma](#)) can lead to chronic impairment of vision. Likewise, sensorineural hearing loss is caused by death or damage to the auditory nerve or to the sound-detecting cells of the inner ear. Many common [auditory](#) and visual disorders are age-related and can reduce independence and quality of life in the elderly. These include [presbycusis](#) (age-related hearing loss), [age-related macular degeneration](#) (loss of central vision), and [cataract](#) (clouding of the lens of the eye).

Dental and Craniofacial Disorders: [Periodontal disease](#) is a disorder of the gingiva and tissues around the teeth. It varies in severity but can lead to bleeding, pain, infection, tooth mobility, and tooth loss. Periodontal disease can affect other organs and has been linked to cardiovascular disease, diabetes, and pulmonary disease. Temporomandibular joint and muscle disorders, commonly called TMJD, are a group of conditions that cause pain and dysfunction in the jaw joint and the muscles that control jaw movement. The primary symptom of these disorders is pain, which can become permanent and debilitating.

Mental Illness: Mental disorders are the leading cause of disability in the United States and Canada. In contrast to many other chronic medical conditions, mental disorders typically begin at an early age, usually before the age of 30. Mental disorders, such as [schizophrenia](#) and [mood disorders](#) including depression and bipolar disorder, are increasingly recognized as chronic medical illnesses of young people. Mental illness also can coexist with a number of other chronic diseases. For example, major depressive disorder, a significant contributor to disability worldwide, can be triggered by chronic diseases such as cancer or stroke in those who are at risk for developing the disorder. Conversely, depression is associated with an increased risk for other diseases such as coronary heart disease and drug addiction.

Addiction to Alcohol and Other **Drugs of Abuse:** The frequent co-occurrence of mental disorders with alcohol dependence and other substance use disorders, including [nicotine addiction](#), makes treating both disorders crucial, albeit challenging. [Addictions to alcohol](#) and [other drugs of abuse](#) are chronic diseases that have both physiological and behavioral components.

Chronic Pain and Palliative Care: [Pain and palliation](#)—care to alleviate the symptoms of disease and improve quality of life without actually curing the disease—are issues associated with many chronic diseases, regardless of the organ system affected. Pain is cited as the most common reason Americans access the health care system; it is a leading cause of disability; and it is a major contributor to health care costs. Low back pain is among the most common complaints, along with migraine or severe headache, and joint pain, aching, or stiffness. Joint pain is most commonly experienced in the knee.¹⁰⁷

¹⁰³ For more information, see http://www.cdc.gov/nchs/data/hestat/preliminarydeaths05_tables.pdf#B.

¹⁰⁴ Ibid.

¹⁰⁵ For more information, see <http://www.nhlbi.nih.gov/health/dci/index.html>.

¹⁰⁶ For more information, see: <http://diabetes.niddk.nih.gov/dm/pubs/gestational/#1>.

¹⁰⁷ For more information, see National Health Interview Survey, 2006, public use data file. Available at:

<http://www.cdc.gov/nchs/nhis.htm>.

Summary of NIH Activities

NIH invests significant resources in the study of chronic diseases. The diverse NIH research portfolio broadly encompasses research on the normal physiology of all organ systems in the body; studies of rare and common diseases in both children and adults; development of devices and technologies for disease detection and diagnosis; evaluation of strategies for prevention and treatment that might be based on pharmaceuticals, behavioral modification, surgical techniques, mechanical devices, or other approaches; and translation of research results into real-world applications or resources for the benefit of patients who live with chronic diseases every day. This section highlights key examples of challenges, progress, and emerging opportunities in NIH-supported research on chronic diseases and organ health.

Understanding Fundamental Mechanisms of Organ Health and Disease

NIH supports a diverse portfolio of basic research to understand the molecular and cellular mechanisms of human physiology in health and disease. Basic science discoveries are critical for generating new insights into disease triggers and risk factors, identifying new targets for therapy, and developing innovative strategies and advanced technologies to prevent, detect, diagnose, and treat chronic diseases and organ damage. For example, scientists have discovered a protein, Roundabout4 (Robo4), which blocks the activity of vascular endothelial growth factor (VEGF). Abnormal activation of VEGF triggers neovascularization—the pathologic growth of new blood vessels—that is characteristic of eye diseases such as age-related macular degeneration and diabetic retinopathy. Thus, Robo4 presents a new target for the development of therapies to prevent or delay vision loss in patients with vascular eye disease. Advances in neurobiology have revealed a connection between brain function and obesity that could point to new weight loss strategies. For example, researchers have discovered that, in response to fat intake, the small intestine releases a factor that subsequently enters the brain and suppresses appetite in rats.

New findings in alcohol research have uncovered molecular mechanisms involved in both the detrimental and beneficial effects of alcohol. Experiments in fruit flies pointed to a role for the epidermal growth factor receptor (EGFR) pathway in mediating sensitivity to alcohol. Researchers also showed that FDA-approved drugs that block the EGFR pathway increased alcohol sensitivity in mice and decreased alcohol consumption in rats, suggesting that these existing drugs might be useful as treatments for alcohol use disorders in humans. Other studies revealed the endocannabinoid pathway as a factor in both diet- and alcohol-induced fatty liver and its metabolic consequences. In addition, researchers identified a molecular pathway that could explain how moderate levels of alcohol consumption protect the heart from ischemic injury, a leading cause of death in developed countries. Development of drugs that target these pathways could lead to new treatments for fatty liver and cardiac ischemia, respectively.

At the level of cellular biology, NIH-supported researchers are making progress in understanding the role of specific cell types in health and disease. For example, scientists have demonstrated that hematopoietic stem cells (HSCs) from bone marrow can direct the differentiation of osteoblasts (cells that build bone) from precursor cells. This finding suggests that HSCs might represent a therapeutic target for treating a variety of bone defects, including osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities. In another example, for many years, scientists believed that metabolically active brown fat could be found only in human infants and in hibernating mammals. Recent findings from NIH-supported research have overturned this longstanding paradigm by

revealing that brown fat cells do in fact persist in adult humans. In contrast to white fat cells that store fat, brown fat cells burn fat to generate heat and, therefore, present a novel target for obesity and weight control therapies.

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Some chronic diseases are associated with the presence of infectious agents that may be either a consequence or a cause of the disease. For example, patients with atopic dermatitis, a common form of eczema, have high levels of bacteria, such as *Staphylococcus aureus*, on their skin, and these patients experience frequent skin infections. Researchers have learned that atopic dermatitis patients exhibit high levels of Th2 cytokines in their skin that prevent the release of an antimicrobial protein that would normally kill the bacteria. Other researchers are studying *Porphyromonas gingivalis*, a bacterium that causes severe, chronic periodontal disease. Using a mathematical technique known as flux-balance analysis, scientists developed a metabolic network map of *P. gingivalis*. This map provides an important tool for predicting how the bacterium would react to perturbation of specific genes or metabolic pathways and will accelerate research to discover new antibacterial drug targets.

NIH is developing new initiatives to capitalize on major breakthroughs and stimulate basic research that will fill gaps in our understanding of a variety of chronic diseases. For example, the NIEHS Director's Challenge Program is advancing research on diseases associated with oxidative stress. The program supports highly collaborative, multidisciplinary teams to study the role of specific genes involved in oxidative stress-induced diseases. Although the program initially will focus on bronchopulmonary dysplasia and retinopathy of prematurity—chronic diseases that affect very low birth weight infants—support for this line of research has the potential to impact a range of diseases, including asthma, cancer, cardiovascular diseases, and neurodegenerative diseases.

Animal models that faithfully mimic human disease or aspects of disease are important tools for understanding fundamental disease mechanisms and for developing new strategies for prevention and treatment. NIH-supported researchers developed a pig model that lacks or has mutations in CFTR, the gene responsible for cystic fibrosis in humans. This new large animal model provides extraordinary opportunities to understand the development of cystic fibrosis in childhood and to test potential therapies. New research grants have been funded to support multidisciplinary research on this unique model of cystic fibrosis.

Detecting and Diagnosing Chronic Disease

Early detection of a chronic disease or organ damage can benefit patients and improve understanding of disease progression in ways that could lead to new strategies for disease prevention. NIH supports research on new methods and technologies for early, accurate, and less invasive detection of chronic diseases. Among the benefits of early disease detection is the opportunity it affords patients to begin to take measures that might prevent disease progression or otherwise improve health outcomes. For example, NIH supports research aimed at evaluating the most effective strategies to improve screening methods to identify youth and adults who have or are at high risk for developing alcohol and other drug use disorders. Related studies focus on understanding what factors, such as the role of parents or families, increase the use and effectiveness of alcohol screening and intervention programs in youth. NIH also provides tools to facilitate the implementation of screening and brief intervention in primary care settings. For example, the [NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test, or NM ASSIST](#) is a Web-based tool that guides clinicians through a short series of

questions for patients and, based on a patient's responses, generates a substance involvement score that suggests the level of intervention needed. The tool also provides links to resources for conducting a brief intervention and treatment referral, if warranted.¹⁰⁸

One benefit of early detection is that it might lead to new insights into the natural history of a disease. NIH and NASA researchers have developed an imaging device that allows clinicians to measure the loss of alpha crystallin protein in the eye, a process that precedes age-related cataract formation. This new imaging technology will help researchers better understand the development of cataracts, a leading cause of adult blindness, and could point to new strategies for prevention of vision loss in cataract patients.

Scientists are developing a new technology that combines magnetic resonance imaging with sound waves to measure the "stiffness" of an internal organ, which could provide diagnostic information without the need for organ biopsy or other invasive techniques.

In addition to early detection, accurate diagnosis of disease is critical to ensuring that a patient's disease is treated promptly and appropriately. For example, scientists are developing a new technology that combines magnetic resonance imaging (MRI) with sound waves to measure the "stiffness" of an internal organ, which could provide diagnostic information without the need for organ biopsy or other invasive techniques.

Often patients, especially those with rare diseases or conditions, seek help from multiple physicians and other health care providers over many years without receiving a definitive diagnosis. NIH has launched a new clinical research program, the [Undiagnosed Diseases Program](#) (UDP), to evaluate patients with longstanding undiagnosed disorders. The UDP capitalizes on the combined knowledge of a team of NIH scientists and medical specialty experts to assist patients who have unknown disorders in achieving an accurate diagnosis, as well as to discover new diseases that provide insight into human biology. In its first year, 158 patients with undiagnosed medical conditions were accepted into the program.

NIH has launched a new clinical research program, the Undiagnosed Diseases Program, to evaluate patients with longstanding undiagnosed disorders.

¹⁰⁸ The screening tool and associated resources are available at <http://www.nida.nih.gov/nidamed/>.

Identifying Risk and Preventing Chronic Disease

A person's risk for developing a chronic disease can depend on multiple factors that include genetic or inherited traits, exposure to environmental toxins, or modifiable behaviors such as diet, smoking, physical activity, or stress. Many chronic diseases are known to result from interactions among genetic, environmental, and behavioral factors, although for most diseases the exact nature of those interactions and the relative importance of the various risk factors remain poorly understood. NIH supports research to identify all types of risk factors, understand the contribution of risk factors to the mechanisms of disease, and apply knowledge of those factors to develop strategies for modifying risk

and preventing disease.

NIH-supported researchers have made significant progress in discovering a diversity of risk factors for common chronic diseases. NIH-supported [Transdisciplinary Tobacco Use Research Centers](#) have explored many variables associated with vulnerability to tobacco addiction and/or cessation, including genetic, familial, cultural, environmental, and comorbidity factors. Research on the effects of environmental exposures has found that certain pesticides are associated with increased risk of type 2 diabetes in individuals who are licensed pesticide applicators. This elevated risk was independent of the age, state of residence, or body mass index of the individual. Several cohort studies of osteoporosis have searched for factors that predict risk of bone fracture in older Americans. For example, researchers using data from the Framingham Osteoporosis Study observed that higher vitamin C consumption is associated with fewer hip fractures, while researchers from the [Women's Health Initiative](#) showed that low blood levels of vitamin D are associated with higher risk of hip fracture. The identification of modifiable risk factors, such as vitamin intake, in these and related studies can inform strategies for diagnosis, prevention, and treatment of osteoporosis in elderly individuals who are most vulnerable to fracture.

Specific population groups as defined by age, sex, race, ethnicity, or an array of other characteristics appear to be at higher risk for some chronic diseases. For these reasons, NIH supports large epidemiologic and clinical studies to identify genetic and nongenetic risk factors in defined populations.

Like osteoporosis, many chronic diseases are associated with a large number of risk factors, some of which have small or variable effects in any single individual. In addition, specific population groups as defined by age, sex, race, ethnicity, or an array of other characteristics appear to be at higher risk for some chronic diseases. For these reasons, NIH supports large epidemiologic and clinical studies to identify genetic and nongenetic risk factors in defined populations. Examples of large population studies to identify risk factors for chronic diseases include:

- Multiple chronic diseases, including heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and others, in people of Hispanic/Latino heritage living in the United States ([Hispanic Community Health Study](#))
- Cardiovascular disease in men and women from four ethnic groups—White, African American, Hispanic, and Chinese ([Multi-Ethnic Study of Atherosclerosis](#))
- Cardiovascular disease in American Indian families ([Strong Heart Study](#))
- Coronary artery disease in Alaskan Natives (Genetics of Coronary Artery Disease in Alaska Natives Study)
- Cardiovascular disease in African American and White young adults who were between 18 and 30 years of age when the study began in 1985 ([Coronary Artery Risk Development in Young Adults Study](#))
- Chronic obstructive pulmonary disease in current and former smokers (Genetic Epidemiology of COPD study)
- Alcohol dependence in extended families that are densely affected by alcoholism ([Collaborative Study on the Genetics of Alcoholism](#))
- Glaucoma in adults (NEI Glaucoma Human Genetics Collaboration)
- Diabetes in youth under 20 years of age in varying ethnic and racial groups ([Search for Diabetes in Youth Study](#))
- Diabetes in families with multiple members affected ([Type 1 Diabetes Genetics Consortium](#)) and several studies of type 2 diabetes, including cohorts from European and Scandinavian populations (e.g., Finland-US Investigation of NIDDM Genetics, Diabetes Genetics Replication and Meta-analysis Consortium) and from multiple ethnic groups ([The Diabetes Prevention Program](#), or DPP)
- Breast cancer, uterine fibroids and endometriosis, rheumatoid arthritis, thyroid disease, asthma,

cardiovascular disease, osteoporosis, Parkinson's disease, age-related cognitive decline, and other diseases in sisters of women who have had breast cancer ([The Sister Study: Environmental Risk Factors for Breast Cancer and Other Diseases](#))

Many chronic diseases have complex genetic contributions, such that susceptibility for a given disease can be influenced by different genes in individual patients or groups of patients. Scientists identified variants of the *MYH9* gene that are associated with chronic kidney disease (CKD) in African Americans and that result from conditions other than diabetes. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition underlies the disorder. In the long term, researchers might be able to predict a person's risk for CKD or their potential to respond to specific therapies depending on whether they carry *MYH9* variants that are associated with the disease.

By understanding the risk factors associated with specific chronic diseases, researchers can design interventions that may prevent or delay onset of these diseases in susceptible individuals. Prevention strategies can address biological, environmental, behavioral, or psychological factors in the development of disease and may be tailored to meet the needs of specific groups or settings. For example, the rate of type 2 diabetes and obesity is increasing among both adults and children in the United States. Previously, the [Diabetes Prevention Program](#) (DPP) showed that either lifestyle modification to promote modest weight loss or treatment with the diabetes drug metformin could prevent or delay the onset of type 2 diabetes in at-risk adults in all participating ethnic groups. A follow-up study, the Diabetes Prevention Program Outcomes Study (DPPOS) is assessing the long-term durability of the DPP interventions, as well as their impact on preventing cardiovascular disease.

NIH is committed to translating the results of carefully controlled clinical trials into strategies for disease prevention and control that will benefit the general public. For example, researchers are evaluating the effectiveness of the [Diabetes Prevention Program](#) (DPP) lifestyle intervention in real-world settings. A recent pilot study suggests that using YMCAs may be a low-cost way to deliver a lifestyle intervention proven to prevent or delay type 2 diabetes to large numbers of people at risk for the disease in the United States. This type of translational research is critical for validating a cost-effective method for prevention of type 2 diabetes on a population-wide scale, especially for those from minority populations that are disproportionately affected by this disease.

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Many chronic illnesses are largely preventable through behavioral changes. For example, tobacco use, insufficient physical activity, and poor eating habits are implicated in many of the most common chronic diseases, including cardiovascular disease, type 2 diabetes, and chronic obstructive pulmonary disease. However, changing unhealthy behaviors can be challenging for many people. To facilitate a more comprehensive understanding of aspects of behavior change across a variety of disciplines, the trans-NIH Committee on the Science of Behavior Change (SOBC) has been established. In June 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 acquiring and preventing particular behaviors, changing existing behaviors, and maintaining desirable behaviors. The committee will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

Prevention of chronic diseases in children and other vulnerable populations is a major focus of NIH

research. For example, clinical research trials to prevent type 2 diabetes and obesity in children are underway. One such study, HEALTHY, is testing a multifaceted approach for prevention of type 2 diabetes risk factors in middle school children. Components of the HEALTHY prevention strategy include changes to school food services and physical education classes, behavioral changes, and communications campaigns. Other researchers are assessing whether development of peanut allergies in at-risk infants and very young children could be prevented by early and regular consumption of peanut-containing snacks. Studies on the prevention of drug abuse in children and adolescents are evaluating innovative approaches, such as physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. The NIH Rapid Response Program supports research to prevent and reduce alcohol use among college students. A variety of prevention approaches are being explored, such as residential learning communities, peer-facilitated alcohol interventions, freshman parent-student initiatives, alcohol screening in college health clinics, and others.

U.S. military personnel, veterans, and their families are at high risk for the onset, exacerbation, or relapse of substance abuse and other mental health problems. NIH has launched initiatives to encourage collaborative research on prevention of alcohol, drug, and tobacco abuse, as well as associated problems such as post-traumatic stress disorder, traumatic brain injury, sleep disturbances, and relationship violence, in military members and their families. The role of trauma and stress in the onset of substance use and abuse in this population is a particular area of research focus.

NIH has launched initiatives to encourage collaborative research on prevention of alcohol, drug, and tobacco abuse, as well as associated problems such as post-traumatic stress disorder, traumatic brain injury, sleep disturbances, and relationship violence, in military members and their families.

NIH awareness campaigns and educational materials are critical tools for keeping the public informed of new findings in prevention research. A recently updated guide, titled [Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging](#), reviews the benefits of physical activity and exercise in combating chronic conditions in older adults. The *Guide* provides specific activities and exercises that can be tailored to an individual's strength and skill level. Additional awareness campaigns and education materials on chronic diseases are described in the section "[Chapter 3: Health Communication and Information Campaigns and Clearinghouses](#)."

Depression frequently occurs among individuals with other medical conditions, such as heart disease, diabetes, and Parkinson's disease. Ongoing NIH-supported research on early detection, prevention, and treatment of depressive disorders—and their relationship to other chronic diseases—can help identify ways to reduce the years lost due to disability as a result of comorbid depression.

Treating Chronic Disease and Comorbidities

Once established, chronic diseases require long-term interventions that frequently involve a combination of medical, surgical, behavioral, or other treatments. For some diseases without effective therapies, symptom management to improve quality of life is the only option. Even when therapies are available for a given disease, those therapies might not be appropriate for all patients. For example, drugs or other treatment approaches used in adult patients have not always been proven to be safe for use in children. Other therapies that have been developed based on specific molecular pathways or genetic mutations might have variable efficacy in individual patients with different genetic backgrounds.

Treatment of comorbid chronic disease presents particular challenges. Notably, individuals with multiple chronic conditions are more likely to endure poor functional status, unnecessary hospitalizations, adverse drug events, duplicative tests, and conflicting medical advice. NIH is committed to addressing the needs of Americans with two or more chronic medical conditions. For example, in 2005, NIH solicited applications on research supporting planning projects for clinical trials that establish a scientific basis for future interventions to improve health outcomes related to interactions of multiple co-occurring conditions in elderly patients. Projects funded under this initiative were active during FY 2008 and included Patient-Centered Care Management for Seniors with Multiple Morbidities, Walking Activity and the Burden of Multiple Morbidities, Nursing Home Comorbid Depression Care Management, Osteoporosis in Women with Rheumatoid Arthritis, and Tailored Clinical Trials for Hypertension and Fall Risk. In another example, scientists are studying how best to treat people with both cystic fibrosis and diabetes. New treatments for cystic fibrosis are helping people live much longer, but this has resulted in an increasing number of people with the disease developing cystic fibrosis-related diabetes. New research has shown that aggressive insulin therapy, begun earlier in the course of diabetes than previously recommended, can help many people with cystic fibrosis-related diabetes maintain their body weight and avoid the excess mortality associated with this comorbidity.

To address the critical medical needs of the American public, NIH pursues a vigorous research agenda to identify, develop, and validate innovative treatments for chronic diseases and organ damage that are safe, efficacious, and cost-effective.

An essential first step in the development of new medical therapies for chronic diseases is the identification of molecules with a desired biologic activity. Preclinical studies in animal models are then conducted to examine safety and efficacy of novel compounds before they are tested in people. NIH supports research that fills important gaps in preclinical drug development that currently are not being addressed by the pharmaceutical industry. For example, laboratories have been established to screen molecules that hold promise for the treatment of alcohol dependence. Other researchers are developing medications for stimulant, cannabis, inhalant, or polysubstance abuse. Such medications might act by diminishing conditioned responses, improving cognitive function (thereby facilitating engagement in cognitive-behavioral therapy), or modifying the brain's response to stress, one of the primary triggers for relapse in people recovering from addiction. Once a candidate drug has been chosen, animal studies can provide a preliminary estimation of risks and benefits. For example, researchers have identified two drugs that increase fat-burning muscle and improve endurance in mice. These drugs could represent new treatments for certain muscle disorders, frailty, obesity, or other conditions that could be improved by exercise. In another example, NIH supports Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases that are developing new therapeutics for cystic fibrosis and related diseases.

In addition to developing novel drugs, NIH investigators are exploring the potential of using drugs with known safety profiles that have been approved for one condition to treat an unrelated disease. For example, animal studies suggest that fenoterol, a drug used for the treatment of pulmonary disease, might be beneficial in patients with congestive heart failure. Modafinil, approved to treat narcolepsy, may be useful in improving cognitive dysfunction, often a barrier to engaging drug abuse patients in addiction treatment. Repurposing existing drugs in this way offers a potential shortcut around the often lengthy and expensive drug development process, resulting in significant time and cost savings.

NIH invests in specialized resources that support the development of medical and nonmedical treatments for chronic diseases. In response to a congressional mandate, NIH established the [Therapeutics for Rare and Neglected Diseases Program](#) (TRND) to bridge the gap between basic research and human testing of new drugs for rare and neglected diseases. TRND is expected to be a highly collaborative effort that will solicit projects from both extramural and intramural investigators for work within the intramural facility. The program expects to test the potential of both novel and

repurposed drugs for new therapeutic applications.

Adherence to available medical or behavioral regimens is another critical element in ensuring the successful management of chronic diseases. Adherence to proven therapies has been found to save lives, reduce morbidity, and improve quality of life, but can be challenging, especially over the long term. Adherence can be a special problem for those with comorbidities who often must follow complicated regimens consisting of multiple medications. NIH supports several research programs aimed at improving adherence to treatment regimens for chronic diseases, including both medication and behavioral regimens. For example, NIH funded several initiatives that target different aspects of the clinical care system that play a role in facilitating or hindering adherence: One initiative focused on testing innovative yet practical interventions to improve *patient* adherence to treatment for chronic diseases such as hypertension, coronary heart disease, and asthma; another supported studies evaluating novel strategies to improve *clinician* adherence to guidelines for treatment of heart, lung, or blood diseases; and a third (which is still ongoing) is evaluating clinically feasible interventions to effect changes in *medical care delivery systems* to improve hypertension management and prevent complications in African Americans.

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NIH-supported investigators are conducting clinical research and intervention trials to evaluate the safety and efficacy of treatments for a wide range of chronic diseases. The examples described below represent only a fraction of the research on drugs, surgical techniques, behavioral therapies, and other strategies for the treatment of chronic diseases within the NIH portfolio. Information about these and other NIH-supported clinical trials is available at the clinicaltrials.gov website.

- *Chronic Obstructive Pulmonary Disease (COPD)*: The Long-Term Oxygen Treatment Trial is evaluating the safety and effectiveness of home oxygen therapy for patients with COPD and moderately severe hypoxemia (low blood oxygen levels).
- *Idiopathic Pulmonary Fibrosis (IPF)*: The Idiopathic Pulmonary Fibrosis Clinical Research Network is exploring treatments for patients with newly diagnosed IPF using combinations of existing and relevant drugs given at multiple points in the disease process. The first clinical trial within this network to treat pulmonary hypertension in patients with advanced IPF has been completed. Two additional trials are testing other forms of IPF therapy, including single-agent or combination treatment with corticosteroids, azathioprine, and N-acetylcysteine, as well as oral anticoagulation therapy for fibrosis progression.
- *Obstructive Sleep Apnea (OSA)*: The [Apnea Positive Pressure Long-Term Efficacy Study](#) is assessing the role of nasal continuous positive airway pressure (CPAP) in alleviating cognitive impairment associated with OSA. The Impact of CPAP on Functional Outcomes in Milder Obstructive Sleep Apnea study is evaluating the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. The results of both multicenter trials are expected to be released in 2010.
- *Diabetic Cardiovascular Disease*: The [Action to Control Cardiovascular Risk in Diabetes](#) (ACCORD) trial was designed to assess whether the rate of major cardiovascular disease events in persons with longstanding type 2 diabetes and who have cardiovascular disease or two or more risk factors for developing it 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. In this trial, the intensive group aimed to lower blood sugar levels to be similar to those found in adults without diabetes, whereas the standard group had a target similar to what is

achieved, on average, by individuals treated for type 2 diabetes in the United States. The intensive blood glucose management was stopped early due to evidence of higher mortality among people in the intensive group compared with those who received the current standard of care. The blood pressure and lipid components of the trial proceeded as designed.

- *Diabetic Retinopathy*: The collaborative [Diabetic Retinopathy Clinical Research Network](#) facilitates multicenter clinical research of diabetic retinopathy and macular edema. Approximately two-thirds of the 117 sites are community-based practices, representing about a third of the U.S. retina specialists in 38 states and involving more than 1,300 health care practitioners. In collaborations with industry, the network compares the effectiveness of surgical, drug, and laser therapies and examines the diagnostic potential of new imaging tools.
- *Type 2 Diabetes*: The [Look AHEAD](#) (Action for Health in Diabetes) trial is examining the long-term health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss in overweight or obese adults with type 2 diabetes. Results from the first year of the trial showed that clinically significant weight loss could be achieved through an intensive lifestyle intervention, and that this weight loss was associated with improvements in health-related quality of life, cardiovascular fitness, blood pressure, cholesterol, and blood glucose.
- *Attention Deficit Hyperactivity Disorder (ADHD)*: The Multimodal Treatment Study of Children with ADHD reported that treatment with stimulant medication alone or in combination with psychosocial/behavioral treatment was more effective than behavioral treatments alone or routine community care in reducing the symptoms of diagnosed ADHD in elementary school children. A follow-up study continues to observe long-term outcomes in study participants as they enter adolescence and early adulthood.
- *Functional Gastrointestinal (GI) Disorders*: Several clinical trials are underway to improve the diagnosis and treatment of functional GI disorders. For example, the Functional Dyspepsia Treatment Trial is testing the use of antidepressants for functional dyspepsia (indigestion). Antidepressant therapy also is being tested as a treatment for gastroparesis, the slow movement of food from the stomach to the intestinal tract. A short-term behavioral treatment is being evaluated in patients with irritable bowel syndrome.
- *Asthma*: The NIH Inner-City Asthma Consortium is conducting multiple studies of immune-based therapies to prevent and treat asthma in inner-city children. One ongoing trial is investigating the safety, dosing level, and biologic activity of a potential immunotherapy for cockroach allergen, a major determinant of asthma severity in this population.
- *Liver Diseases*: NIH supports clinical research on multiple liver diseases that affect children and adults. For example, the [Nonalcoholic Steatohepatitis \(NASH\) Clinical Research Network](#) is conducting placebo-controlled trials of potential NASH therapies, including pioglitazone or vitamin E in adult patients and metformin or vitamin E in children. Adult and pediatric Acute Liver Failure Study Groups are evaluating potential therapies to improve survival of patients with acute liver failure due to drugs or other factors.
- *Pelvic Floor Disorders*: The [Pelvic Floor Disorders Network](#) investigates new prevention and treatment strategies for pelvic floor disorders, which affect nearly one-quarter of all women in the United States. In one network trial, researchers demonstrated that a two-step surgical procedure, compared to standard practice, could halve the incidence of urinary incontinence in women with pelvic floor prolapse. Another group of researchers conducted the Program to Reduce Incontinence by Diet and Exercise. This study showed that weight loss could reduce the frequency of urinary incontinence in overweight and obese women.
- *Alcohol Dependence*: NIH is establishing a multicenter network to conduct Phase II trials for treatment of alcohol dependence. Quetiapine and levetiracetam are examples of drugs being tested by the network. In a trial conducted by another group of investigators, alcohol-dependent patients who recently had stopped drinking were given a drug that blocks a brain chemical involved in response to stress. Patients treated with this drug experienced reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones.
- *Obesity*: The [Longitudinal Assessment of Bariatric Surgery \(LABS\)](#) consortium is evaluating the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. A related observational study, Teen-LABS, is collecting data on bariatric surgery in obese adolescents to

- determine whether surgery is an appropriate treatment option in that age group.
- *Dental Disease*: Three [dental practice-based research networks](#) have been launched to train practicing dentists in clinical research and expand the evidence base in dentistry. One area of focus for the networks is testing new treatment strategies for dental caries (tooth decay), which is a common chronic condition in youth.
 - *Age-Related Macular Degeneration (AMD) and Cataract*: Following up on the successful multicenter [Age-Related Eye Disease Study \(AREDS\)](#), which showed high-dose antioxidant supplements can slow the progression of AMD, [AREDS 2](#) will test oral supplementation of lutein/zeaxanthin and omega-3 fatty acids for the prevention of AMD and cataract.
 - *End-Stage Renal Disease (ESRD)*: Patients being treated with hemodialysis for ESRD (kidney failure) often undergo a procedure to create a site on the body that allows easy, frequent access to blood vessels. Over time, these access sites can become unusable. The Dialysis Access Consortium found that treatment with an anti-clotting drug did not improve long-term usability of fistulas, one type of access site. Separately, the consortium showed that a combination of aspirin and another anti-clotting drug could improve the long-term usability of another access site type, known as a graft. The new Vascular Biology of Hemodialysis Vascular Access Consortium will study the basic mechanisms of vascular access failure, a line of research that could inform future strategies to improve outcomes in ESRD patients.
 - *Substance Abuse*: Computer-Based Training for Cognitive Behavioral Therapy is a computer-based training program that focuses on teaching basic coping skills, presenting examples of effective use of coping skills in a number of realistic situations in video form, and providing opportunities for patients to practice and review new skills while receiving substance abuse treatment. This delivery of cognitive behavioral therapy appears to have both short-term and enduring effects in reducing drug use. Such technology increasingly will be harnessed as a low-cost option to provide evidence-based addiction treatments and broaden their availability.

As a public agency, NIH has a particular interest in comparative effectiveness research (CER), which compares two or more treatments for a given condition to determine which treatment is most effective in “real-world” settings.¹⁰⁹ For example, the Acute Renal Failure Trial Network studied patients with acute kidney failure and failure of at least one other organ or a serious infection. Network researchers found no survival benefits from an intensive dialysis regimen compared to conventional dialysis. This finding could spare critically ill patients from unnecessary medical interventions. The Comparison of AMD Treatments Trials (CATT): Lucentis-Avastin Trial is assessing the relative safety and efficacy of two FDA-approved drugs in the treatment of age-related macular degeneration (AMD). One drug, Lucentis™, was specifically approved for AMD treatment and costs around \$2,000 per month. A second drug, Avastin®, originally was approved for treatment of colorectal cancer, but its similarity to Lucentis™ has led some clinicians to use Avastin® to treat AMD patients. Because Avastin® costs approximately \$100 per month, rigorous evidence that the benefits and risks of Lucentis™ and Avastin® are comparable could result in significant health care cost savings. Additional information regarding NIH’s CER-related activities can be found in *Chapter 3: Clinical and Translational Research*.

As a public agency, NIH has a particular interest in comparative effectiveness research, which compares two or more treatments for a given condition to determine which treatment is most effective in “real-world” settings. The Comparison of AMD Treatments Trials: Lucentis-Avastin Trial is assessing the relative safety and efficacy of two FDA-approved drugs in the treatment of age-related macular degeneration.

Comparative effectiveness research can reveal that a one-size-fits-all approach to treating disease is not always appropriate. In some cases, carefully defined subgroups of patients may benefit more—or experience higher risks—from certain treatments than other patients. The BARI 2D trial compared management strategies for patients with stable coronary artery disease and type 2 diabetes. The goal was to determine whether mortality and cardiovascular disease 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 cardiovascular disease event rates. However, in a subgroup of patients for whom bypass surgery was deemed appropriate, prompt revascularization did reduce the rate of major, nonfatal cardiovascular events.

For many patients with severe organ damage due to chronic disease or injury, the only viable, long-term treatment option is organ transplantation. NIH supports a range of research programs to improve organ transplantation procedures, develop strategies for immune tolerance that could preclude the need for lifelong immunosuppression in transplant patients, and increase the supply of organs for transplantation. The Clinical Trials in Organ Transplantation (CTOT) program was established to improve organ transplantation outcomes by conducting both clinical and mechanistic studies. In one CTOT study, investigators developed a protocol for kidney transplantation and immunosuppressive therapy that allowed 4 out of 5 patients to discontinue all immunosuppressive drugs after 9 to 14 months without rejection of the transplanted kidney. In the area of pediatric liver transplantation, the Childhood Liver Disease Research and Education Network is exploring treatment options for children with liver diseases or who have undergone liver transplantation. Another network is planning a study of immunosuppression minimization in children after liver transplantation. Another major effort, the [Immune Tolerance Network](#), is developing new approaches to establishing immune tolerance in patients who have undergone kidney, liver, or pancreatic islet transplantation. Importantly, immune tolerance strategies for transplantation could have applications in the treatment of asthma, allergies, and autoimmune diseases, including type 1 diabetes, multiple sclerosis, and lupus erythematosus.

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Organ transplantation has been a life-changing—oftentimes, life-saving—procedure for countless patients with chronic disease. However, many patients who could potentially benefit from a transplant are not able to receive one due to shortages of suitable organs for transplantation. The Cornea Donor Study demonstrated that corneal transplants using tissue from 66- to 75-year-old donors have success rates similar to transplants using tissue from 12- to 65-year-old donors. Because corneal tissue from donors ages 65 and older traditionally has been rejected for transplantation purposes, this result has the potential to expand the pool of cornea donors and ensure an adequate supply of tissue for transplantation.

The use of complementary and alternative medicine (CAM) is common among the American public. The 2007 National Health Interview Survey found that 38 percent of adults and 12 percent of children use some form of CAM, such as nonvitamin/nonmineral natural products, deep breathing, meditation, massage therapy, and yoga. NIH supports a substantial research effort to provide evidence-based evaluation of the safety and efficacy of CAM practices. For example, the Glucosamine/Chondroitin Arthritis Intervention Trial assessed the use of these dietary supplements to treat pain and reduce structural damage associated with knee osteoarthritis. Researchers discovered that combined glucosamine/chondroitin sulfate treatment did not provide significant pain relief among study participants overall; however, a subgroup of subjects with moderate to severe pain did experience significant relief. Treatment with the supplements alone or in combination did not improve loss of cartilage in osteoarthritis of the knee compared to a placebo.

¹⁰⁹ This definition of “comparative effectiveness research” is adapted from Federal Coordinating Council for Comparative Effectiveness Research, *Report to the President and the Congress, June 20, 2009*. Available at:

<http://www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf>.

Addressing Pain and Palliative Care in Chronic Diseases

Many chronic diseases are associated with pain that can be chronic and severe. Pain often is difficult to treat and can significantly erode patients' quality of life. NIH supports a spectrum of pain research that includes basic science to understand the mechanisms of pain and pain relief, as well as clinical research to evaluate pharmacological, surgical, and alternative strategies for pain management. For example, researchers have identified two enzymes of the matrix metalloprotease family that are involved in the early development and persistence of chronic neuropathic pain due to nerve injury. Other researchers have discovered ways to selectively activate the cannabinoid system to provide pain relief without the effects on mental function and abuse potential that are common to opioid-based analgesics. Both findings will inform ongoing research to develop safe, effective, and nonaddictive drugs for pain relief. At the clinical level, NIH-supported researchers are testing the effectiveness of nonpharmacological approaches for the treatment of chronic low back pain. The Spine Patient Outcomes Research Trial (SPORT) showed that surgery is more effective than nonoperative treatments, such as medications and physical therapy, for the most common causes of chronic, severe low back pain.

Impressive progress has been made in recent years in understanding the mechanisms of pain and developing treatments, especially for common conditions such as low back pain. However, little is known about the biological mechanisms of pain in rare conditions, such as sickle cell disease, that are associated with lifelong, often severe pain. NIH launched an initiative, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to foster basic and translational research on the unique aspects of pain in this disease. The initiative encourages multidisciplinary approaches that bring together experts in relevant fields, including neurobiology, hematology, pharmacology, and psychology.

Some patients with chronic pain turn to alternative therapies. For example, in a recent study, investigators compared the efficacy of acupuncture with either standardized or customized needle placement, "simulated acupuncture" without skin puncture, and conventional care for chronic low-back pain. After 8 weeks, participants in all 3 acupuncture groups improved their dysfunction scores significantly more than the group receiving usual care. Notably, simulated acupuncture was as effective as acupuncture with either standardized or customized needle placements, raising intriguing questions about the mechanisms by which acupuncture relieves pain.

Palliative care, which includes pain management, focuses on alleviating disease symptoms and improving patients' quality of life. Optimizing end-of-life care is an important topic within the field of palliative care research, particularly with respect to understanding the needs of dying children with chronic diseases and their families. Researchers also are studying the many cultural, spiritual, age-related, and disease-specific factors that affect the end of life. Because each person's experience at the end of life is unique, NIH has developed an initiative to support research on interventions for end-of-life and palliative care that can be applied in a variety of settings, illnesses, and cultural contexts.

A Commitment to Global Health

Chronic diseases take a substantial toll on public health and well-being across the globe. According to the World Health Organization, chronic diseases account for 60 percent of deaths worldwide; fully 80 percent of chronic disease-related deaths occur in low- and middle-income countries (LMICs). The

number of deaths from chronic disease in these countries is double the number of deaths resulting from infectious disease (including HIV/AIDS, malaria, and tuberculosis), maternal and perinatal conditions, and nutritional deficiencies combined. Furthermore, the burden of chronic disease in the developing world is projected to rise dramatically in the coming decades. This increasing burden can be attributed to a number of factors, including longer average lifespan, tobacco use, decreasing physical activity, and increasing consumption of unhealthy foods.¹¹⁰

NIH is committed to addressing this global health problem with a variety of approaches that include support for international research projects and initiatives to build research capacity in LMICs. For example, the NIH-supported [International Tobacco and Health Research and Capacity Building Program](#) demonstrated that smoking was associated with 6- and 8-year reductions in median survival for men and women in India, respectively. This project provided important data on the smoking epidemic in India that can inform public health efforts to educate people in that country on the effects of smoking. In June 2009, NIH joined the [United Health Chronic Disease Initiative](#) and established a network of 11 Collaborating Centers of Excellence in LMICs to build sustainable programs to combat chronic cardiovascular and lung diseases. Each center pairs a research institution in a developing country with at least one academic institution in a developed country.

Future NIH research directions in global health will be informed by a 2009 report of the Institute of Medicine (IOM), [The U.S. Commitment to Global Health: Recommendations for the Public and Private Sector](#).¹¹¹ This report, which updates a 1997 IOM report, lays out arguments for public and private investment in global health and presents key recommendations to guide such investments. Notably, the report calls for additional resources and the adoption of clear health goals to guide the allocation of funds targeted at the reduction of the burden of noncommunicable disease.

Future NIH research directions in global health will be informed by a 2009 report of the Institute of Medicine (IOM). The U.S. Commitment to Global Health: Recommendations for the Public and Private Sector.

Addressing the steady increase in chronic noncommunicable diseases around the world requires a well-trained research workforce with the expertise to study these diseases and their treatments in low- and middle-income countries (LMICs). The new [Millennium Promise Awards: Noncommunicable Chronic Diseases Research Training Program](#) supports research training for scientists in LMICs with a focus on cancer, cerebrovascular disease, lung disease, and obesity. The program encompasses a broad range of research, from understanding genetic and lifestyle factors in the development of chronic diseases to the translation of research outcomes into public health programs and policies that are culturally relevant and sensitive.

¹¹⁰ Daar AS, et al. *Nature* 2007;450(7169):494-6. PMID: 18033288.

¹¹¹ IOM. Board on Global Health. [The U.S. Commitment to Global Health: Recommendations for the Public and Private Sector](#). Washington DC: The National Academies Press; 2009.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRAG = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Understanding Fundamental Mechanisms of Organ Health and Disease

New Therapeutic Target for Macular Degeneration and Diabetic Retinopathy

Discovered: Neovascularization is the term used to describe the growth of abnormal new blood vessels. In some diseases, such as age-related macular degeneration or diabetic retinopathy, neovascularization mistakenly activates and becomes a major pathologic feature. The abnormal vessels leak fluid and serum, which damages the light-sensitive photoreceptor cells in the retina, causing severe and irreversible vision loss. NIH-sponsored research is focused on understanding the pathways that inhibit and promote neovascularization. Previous studies have established that a protein called vascular endothelial growth factor (VEGF) spurs neovascularization, and several therapies have been developed to prevent the abnormal activation of VEGF. A recent NIH-supported study reported the discovery of Roundabout4 (Robo4), a protein that stabilizes the existing vasculature and prevents neovascularization by inhibiting VEGF activity. Robo4 is among a family of Roundabout proteins that previously were found to act as guidance receptors for developing neurons in the nervous system. That Robo4 plays a different and central role in controlling neovascularization represents a breakthrough that may lead to new treatments to prevent or delay the sight-threatening consequences of vascular eye diseases.

- Jones CA, et al. *Nat Med* 2008;14(4):448-53. PMID: 18345009.
- For more information, see <http://www.nature.com/nm/journal/v14/n4/full/nm1742.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) **(NEI)**

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

- Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.
- Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85. PMID: 18249177. PMCID: PMC2442478.
- Gillum MP, et al. *Cell* 2008;135(5):813-24. PMID: 19041747. PMCID: PMC2643061.

Weller CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.

- For more information, see <http://www3.niddk.nih.gov/fund/other/neuroimaging2008/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDDK)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

- Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
- Trim RS, et al. *Alcohol Clin Exp Res* 2009;33(9):1562-70. PMID: 19485971.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIAAA)

Research and Treatment of Drug-Induced Liver Disease: Drug-induced liver toxicity is increasing in the United States and has serious consequences for individuals and society. Alcohol- and diet-induced fatty liver are major causes of morbidity, and knowledge of the mechanisms involved is incomplete. NIH has implemented major research initiatives to study basic liver function, to determine how alcohol and drug abuse cause liver injury and disease, and to develop new medications for treatment of liver disease. For example, NIH researchers are beginning to shed light on the molecular mechanisms of fatty liver, demonstrating that specific chemical messengers (known as endocannabinoids) and their receptors contribute to both diet- and alcohol-induced fatty liver and its metabolic consequences. These and related studies suggest that endocannabinoid receptors could be targeted selectively in drug development for treatment of fatty liver and impaired blood sugar regulation. NIH also has implemented the Drug-Induced Liver Injury Network (DILIN). This network facilitates research on liver toxicity due to prescription drugs or complementary and alternative medicines. Current studies are developing better tools for diagnosing, and ultimately preventing, drug-induced liver injury, as well as enhancing knowledge of liver disease processes. The network has evolved into a resource on drug-induced liver toxicity for the national clinical community and the public.

- Jeong WI, et al. *Cell Metab* 2008;7(3):227-35. PMID: 18316028.
- Osei-Hyiaman D, et al. *Clin Invest* 2008;118(9):3160-9. PMID: 18677409. PMCID: PMC2491458.
- For more information, see <https://diln.dcri.duke.edu/>
- (E/I) (NIAAA, NIDDK)

Beneficial and Harmful Actions of Alcohol on the Heart Involve Alcohol-Metabolizing

Enzyme: Cardiac ischemia, damage to heart muscle caused by reduced or blocked blood flow, affects nearly 1 million people in the United States annually and is the leading cause of death in developed countries. The beneficial effects of moderate levels of alcohol consumption on the heart have been well-documented, and may significantly protect the heart against ischemic injury. Protection involves a preconditioning-like mechanism through activation of the molecule protein kinase C epsilon (PKCe), or prior exposure to certain chemicals such as ethanol, but the underlying molecular targets of this protection remain obscure. Recently researchers showed that in response to ethanol treatment or PKCe activation, the activity and phosphorylation of aldehyde dehydrogenase-2 (ALDH2), the main enzyme that mediates elimination of alcohol from the body, increased and correlated with cardioprotection in rat hearts. A related study showed PKCe moves to the mitochondria where it binds to ALDH2 and, through multiple pathways, significantly reduced ischemic injury. A screen for small molecules that could activate ALDH2 recently identified one with therapeutic potential for individuals subject to cardiac ischemia, including during coronary bypass surgery.

In contrast to the cardioprotective effects observed with moderate alcohol consumption, chronic heavy consumption can cause alcoholic cardiomyopathy (disease of the heart muscle) with hallmark features of abnormal heart enlargement and compromised contractility of heart muscle. Current investigations link acetaldehyde toxicity (a by-product of alcohol metabolism) to alcoholic cardiomyopathy and demonstrate that increased levels of ALDH2 can reduce these effects.

- Churchill EN, et al. *J Mol Cell Cardiol* 2009;46(2):278-84. PMID: 18983847. PMCID: PMC2675554.
Doser TA, et al. *Circulation* 2009;119(14):1941-9. PMID: 19332462. PMCID: PMC2740924.
Chen CH, et al. *Science* 2008;321(5895):1493-5. PMID: 18787169. PMCID: PMC2741612.
- (E) (NIAAA)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell Niche:

Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

- Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

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 SALSalate 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.

- Cypess AM, et al. *N Engl J Med* 2009;360(15):1509-17. PMID: 19357406. PMID: PMC1986615.
- Tseng YH, et al. *Nature* 2008;454(7207):1000-4. PMID: 18719589. PMID: PMC2745972.
- Seale P, et al. *Nature* 2008;454(7207):961-7. PMID: 18719582. PMID: PMC2583329.
- For more information, see <http://tinsalt2d.org/>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK)

Atopic Dermatitis: Investigations in the molecular pathways leading to atopic dermatitis, the most common form of eczema, have identified defects in the skin's protective mechanisms against pathogenic microbes and inflammation-associated immune responses. Researchers have learned that the skin of atopic dermatitis patients is heavily colonized by bacteria, such as *Staphylococcus aureus*, and they have frequent skin infections. Atopic dermatitis patients also have high levels of the messenger molecules, Th2 cytokines, in their skin, which are involved in immune function. These concentrations in atopic dermatitis patient skin have been found to inhibit the release of an antimicrobial protein, human beta-defensin 3, that can kill *S. aureus*. As well, breakdown of skin's barrier function may be a contributor to the disease. The failure of skin integrity allows environmental factors to trigger inflammatory signals that provoke asthma symptoms in a mouse model, and may provide an explanation for the occurrence of asthma in 50 percent of pediatric atopic dermatitis cases. In addition, molecular pathways, which are triggered by bacterial infections in the skin and drive inflammation in atopic dermatitis, have been identified. These genetic and biochemical studies provide important therapeutic targets for the development of treatments to interrupt aberrant disease mechanisms.

- He R, et al. *Proc Natl Acad Sci U S A* 2007;104(40):15817-22. PMID: 17893340. PMID: PMC2000444.

Kisich KO, et al. *J Allergy Clin Immunol* 2008;122(1):62-8. PMID: 18538383.
He R, et al. *Proc Natl Acad Sci U S A* 2008;105(33):11875-80. PMID: 18711124. PMCID: PMC2575291.
Jin H, et al. *J Clin Invest* 2009;119(1):47-60. PMID: 19075398. PMCID: PMC2613448.

- (E) (NIAMS)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

- Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NIDCR)

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 hyperoxia-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, cancer, cardiovascular disorders, and neurodegenerative diseases.

- This example also appears in Chapter 3: Genomics and Chapter 3: Clinical and Translational Research
- (I) (NIEHS)

New Pig Model of Cystic Fibrosis: An NIH-supported research team has generated pigs that lack the CFTR gene, which is responsible for the disease, or possess one of its common mutations. The newborn piglets without CFTR have presentations at birth and shortly thereafter that are similar to those seen in human infants with cystic fibrosis (CF), including typical abnormalities in the intestines, pancreas, and liver. As with human infants, the piglets lacking CFTR do not exhibit obvious lung abnormalities at birth. However, they have the typical ion transport properties of CF airway epithelia and are expected to develop the progressive lung changes over time seen in humans. The development of this pig model represents a major breakthrough in research on cystic fibrosis. In addition to offering unprecedented opportunities to understand how the respiratory disease develops during early childhood, it will allow testing of new preventive and therapeutic strategies. In 2008 and 2009, NIH funded two multidisciplinary program project grants to advance study of this new large-animal model for CF. The research will advance understanding of the pathogenesis and pathophysiology of airway disease and spur development of gene therapy and other pharmacologic approaches for CF lung disease.

- Rogers CS, et al. *Science* 2008;321(5897):1837-1841. PMID: 18818360. PMCID: PMC2570747.
- (E) (NHLBI, NIAID, NIDDK)

Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFS): The multisystemic nature of CFS requires multidisciplinary and interdisciplinary efforts that cut across the missions of all NIH ICs. NIH coordinates CFS research through a Trans-NIH Working Group for Research of Chronic Fatigue Syndrome (CFSWG). The CFSWG is guided by an action plan centered on enhancing the status of CFS research at NIH and among the external and intramural scientific communities. NIH funded a diverse range of projects that hold promise for developing biological markers and potential treatments for CFS and issued new funding opportunities. The first annual meeting of principal investigators whose research projects are specific to understanding the relationship of neuroimmune mechanisms and CFS was held to foster an interdisciplinary collaboration to accelerate research in this area of science through a consortium. Investigators participated in creative team-building that was focused on integrating their research with the hypothesis that an original infectious insult might affect and perpetuate the many symptoms of CFS. Planning is underway for a follow-up workshop that will be expanded to include other CFS researchers.

- For more information, see <http://orwh.od.nih.gov/cfs.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-246.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-247.html>
- (E) (ORWH, NCCAM, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIDCR, NIEHS, NIMH, NINDS, NINR, OBSSR, ODP/ODS)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain

development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

- Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590. PMID: PMC2148343.
- For more information, see <http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (I) (NIMH)

Detecting and Diagnosing Chronic Disease

Screening and Brief Intervention: Given the pervasiveness of high-risk drinking and the high prevalence of alcohol dependence occurring among young adults, efforts to alter drinking trajectories at this stage have life-changing potential and significantly can reduce the burden of illness resulting from alcohol-related problems. NIH actively is engaging the medical community to increase the number of primary care and mental health clinicians who advise, counsel, and treat their patients regarding harmful patterns of alcohol use, including alcohol dependence. NIH continues to promote and disseminate *The Clinician's Guide: Helping Patients Who Drink Too Much* and the associated online training modules. For individuals with milder forms of dependence, who are much less likely to seek any form of alcohol treatment, the integration of alcohol screening and brief intervention into primary care is a cost-effective way to ensure that they receive appropriate care early in the course of their disease. NIH now is exploring other venues for delivery of screening and brief intervention such as emergency departments and college student health centers. Other research objectives are to test strategies to improve screening methods to identify youth with or at high risk for alcohol-related problems, and to test the effectiveness of novel methods to prevent or delay the initiation of alcohol use and decrease the risk for development of alcohol use disorders among youth. Several of these studies examined the effectiveness of interventions that involve parents/families. Other studies focus on what factors increase use and effectiveness of alcohol screening and brief intervention in various settings.

- Schaus J, et al. *J Stud Alcohol Drugs* 2009;16:131-141. PMID: 19538921. PMID: PMC2701092.
- Schaus J, et al. *J Stud Alcohol Drugs* 2009;16:34-44. PMID: 19538911. PMID: PMC2701091.
- Nielsen P, et al. *J Subst Abuse Treat* 2008;35(2):184-201. PMID: 18083321.
- Academic ED SBIRT Research Collaborative. *Ann Emerg Med* 2007;50(6):699-710.e6. PMID: 17870206.
- Chun TH, et al. *Pediatr Emerg Care* 2008;24(10):668-72. PMID: 19242135.
- Sindelar-Manning H, et al. *Pediatr Emerg Care* 2008;24(7):457-61. PMID: 18580703.
- Roudsari B, et al. *Ann Emerg Med* 2009;54(2):285-93. PMID: 19250705. PMID: PMC2745201.
- For more information, see http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm
- For more information, see http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/CME_CE.htm

- (E) (NIAAA)

Reaching Out to Teens and Health Care Professionals: In the spring of 2009, NIDA unveiled NIDAMED, its first comprehensive physicians' outreach initiative. NIDAMED gives medical professionals a variety of information, including tools and resources, to help in screening patients for tobacco, alcohol, and illicit and nonmedical prescription drug use. The NIDAMED website contains links to numerous resources for health care professionals: an online screening tool titled NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST); two guides for clinicians (quick reference and a comprehensive resource guide); a number of key NIDA publications, such as the *Principles of Drug Abuse Treatment: A Research-Based Guide*, *The Science of Addiction*, *a Commonly Abused Drugs Chart*, and a postcard that encourages patients to "Tell Your Doctor About All the Drugs You Use." The NIDAMED initiative stresses the importance of the patient-doctor relationship in identifying and intervening early in patients' drug use behaviors before they evolve into life-threatening conditions. NIH is planning to hold its third annual Drug Facts Chat Day in November 2009. These events let students and teachers in classrooms across the United States ask questions of the Nation's top experts in the field of drug abuse and addiction. NIH staff will gather in a computer lab on the event day and will respond to submitted questions in real time. Chat Day events have proven to be a resounding success. The inaugural event elicited more than 35,000 questions.

- For more information, see <http://www.nida.nih.gov/nidamed>
- For more information, see <http://www.nida.nih.gov/scienceofaddiction>
- For more information, see <http://www.drugabuse.gov/chat>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NIDA)

A New Imaging Device for Early Detection of Cataract: A transparent ocular lens is essential to vision. Cataract (clouding of the lens) remains the primary cause of blindness in the world today. Age-related cataract, the most common type of cataract, is caused by abnormal aggregation of lens proteins that clouds the lens. In the last few years, it has been established that a particular lens protein, alpha crystallin, prevents other lens proteins from aggregating and probably plays a major role in preventing cataract formation. Humans are born with a fixed amount of alpha crystallin, so age-related cataracts occur when the supply is depleted. Researchers at NIH and NASA collaborated to develop a new imaging device that allows clinicians to detect and quantify the amount of unbound alpha crystallin protein in a patient's eye. The device uses dynamic light scattering to measure the amount of alpha crystallin remaining in the lens. This may lead to a better understanding of the early stages of protein aggregation before cataracts form that impinge on vision. Early detection of lens protein disruption may provide clues to preventive treatments that could delay the need for cataract surgery.

- Datiles MB, et al. *Arch Ophthalmol* 2008;126(12):1687-93. PMID: 19064850. PMCID: PMC2600622.
- For more information, see <http://archophth.ama-assn.org/cgi/content/full/126/12/1687>
- This example also appears in Chapter 3: *Technology Development*
- (I) (NEI)

Feeling Organs with Imaging: MRI is known for providing exquisite anatomical images of internal organs. Using a new technique that involves imaging while pushing on an organ with sound waves,

researchers are able to feel the stiffness of internal organs. Because tumors often are more stiff than normal tissue (think, for example, of feeling for a "lump" of stiffer tissue in the breast), this technique may provide important diagnostic information about disease. Initially, this technique is being used to examine the stiffness of liver and potentially provide an alternative to liver biopsy for the 170 million individuals worldwide who live with chronic hepatitis C, a major cause of liver disease.

- Venkatesh SK, et al. *AJR Am J Roentgenol* 2008;190:1534-40. PMID: 18492904.
- Yin M, et al. *Magn Reson Med* 2007;58:346-53. PMID: 17654577.
- Yin M, et al. *Clin Gastroenterol Hepatol* 2007;5:1207-13. PMID: 17916548. PMID: PMC2276978.
- Kruse SA, et al. *Neuroimage* 2008;39:231-7. PMID: 17913514. PMID: PMC2387120.
- For more information, see <http://www.nibib.nih.gov/HealthEdu/eAdvances/28Aug08>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIBIB)

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.

- For more information, see <http://rarediseases.info.nih.gov/Resources.aspx?PageID=31>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (ODP/ORDR, CC, NHGRI, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIMH, NINDS, NINR)

Primary Immune Deficiency Diseases: Primary immune deficiency diseases (PIDDs) are caused by inherited defects in specific cells of the immune system. Individuals with PIDDs generally have an increased susceptibility to infections and may have other medical problems that include autoimmune diseases, deteriorating lung function, tumors, and failure to thrive. Approximately 500,000 people in the United States are diagnosed with PIDDs, many of whom are children; many more individuals with PIDDs likely are undiagnosed. The NIH Primary Immune Deficiency (PID) Clinic, established in 2007, provides comprehensive consultations for individuals 6 months and older who have known or suspected PIDDs. Once clinicians determine that a person might benefit from coming to the NIH PID Clinic, he or she will be invited for a thorough examination and diagnostic work-up. After examination, PID Clinic patients and their referring physicians will be given a detailed list of treatment recommendations. NIH clinicians also will follow-up with referring physicians to check on a person's progress and, as needed, make additional recommendations. In a notable science advance, 11 PID Clinic patients with previously unidentified immune diseases obtained a more accurate disease

diagnosis. While the patients received care for their symptoms—including persistent skin infections, acute allergies, and cancer—investigators observed that they all had a mutation in the same gene, DOCK8, which could account for their health problems. Although further study is required to determine if DOCK8 mutations occur in others with similar symptoms, DOCK8 immunodeficiency syndrome may be a new PIDD. Identifying a cause for the disease has provided comfort to some of those diagnosed who had battled an unknown immune disease for years.

- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2009/DOCK8.htm>
- (I) (NIAID)

Identifying Risk and Preventing Chronic Disease

Transdisciplinary Tobacco Use Research Centers (TTURCs)—Alcohol Use and

Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

- For more information, see <http://dccps.nci.nih.gov/tcrb/tturb>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIAAA, NCI, NIDA)

Diabetes and Pesticide Exposure/the Agricultural Health Study: Exposure to certain pesticides increased the risk of diabetes in licensed applicators, according to researchers from NIH. The investigation of applicators enrolled in the Agricultural Health Study is the largest study to date to evaluate potential effects of pesticides on diabetes incidence in adults. Because previous studies using data from the National Health and Nutrition Examination Survey (NHANES) found associations of diabetes with serum levels of persistent organic pollutants, the researchers wanted to know if there was a similar association between diabetes and lifetime exposure to pesticides. Therefore, they evaluated applicators who reported diabetes for the first time in 5-year follow-up telephone interviews, conducted between 1999 and 2003. Previously, applicators had described use of 50 different pesticides, providing information on 2 primary measures: ever use and cumulative lifetime days of use. Of 50 pesticides evaluated, 7 were associated with an increased incidence of diabetes using both exposure measures. Three of these were organochlorine insecticides (aldrin, chlordane, heptachlor), 2 were organophosphate insecticides (trichlorfon, dichlorvos), and 2 were herbicides (alachlor,

cyanazine). The strongest association was with trichlorfon: Applicators who had used the chemical on more than 10 days in their lifetime had a 2.5-fold increase in risk. Pesticide applicators who reported exposure to these pesticides showed an increased risk of diabetes independent of age, state of residence, and body mass index. The increasing burden of diabetes in populations worldwide warrants an improved understanding of the possible relation of diabetes risk to long-term, low levels of pesticide exposure.

- Montgomery MP, et al. *Amer J Epidemiol* 2008;167:1235-46. PMID: 18343878.
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (**NIEHS**, NCI)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

- Cawthon PM, et al. *J Bone Miner Res* 2009;24(10):1728-35. PMID: 19419308. PMCID: PMC2743283.
- Cauley JA, et al. *Ann Intern Med* 2008;149(4):242-50. PMID: 18711154. PMCID: PMC2743412.
- Mackey DC, et al. *JAMA* 2007;298(20):2381-8. PMID: 18042915.
- Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fractur_e.asp
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NIAMS**, NCRR, NHLBI, NIA)

The Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the United States. The study includes 16,000 participants of diverse Hispanic/Latino

background, including Mexican, Cuban, Puerto Rican, and Central/South American. It is designed to identify factors that render these groups either susceptible to or protected from heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney and liver disease, cognitive impairment, and other chronic conditions. Recruitment started in March 2008 in four cities. Variables such as height, weight, and other body measurements; blood pressure; blood lipids and glucose levels; diet; physical activity; smoking; acculturation; socioeconomic status; psychosocial factors; occupational history and exposure; access to and use of health care services; and use of medications and dietary supplements currently are being assessed.

- For more information, see <http://www.csc.unc.edu/hchs>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODP/ODS)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

- For more information, see <http://mesa-nhlbi.org>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
- (E) (NHLBI, NEI)

The Strong Heart Study: The Strong Heart Study was initiated in 1988 to estimate the morbidity and mortality from cardiovascular disease (CVD) in 3 geographically diverse groups of American Indians and to estimate the levels of CVD risk factors in 4,549 adult men and women aged 45-74 in 3 centers. It evolved into a study of large families after a successful pilot study in each center. The original cohort was examined three times and continues to be followed for morbidity and mortality. The family study currently is completing its second examination and has conducted a linkage study of multiple cardiovascular phenotypes.

- For more information, see <http://strongheart.ouhsc.edu>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NHLBI)

Genetics of Coronary Artery Disease in Alaska Natives Study: This is a study of large families of Alaska natives (Eskimos) living in Nome and surrounding villages. Recruitment of 1,214 individuals in approximately 40 families has been accomplished. A genome-wide scan of almost 400 microsatellite markers and linkage analyses with cardiovascular disease risk factors and subclinical disease measures were completed recently to search for relevant genes. Phase II is nearing

completion and will establish surveillance of the cohort, add four villages that were part of a previous study following a similar protocol, conduct a second examination on the cohort, and pursue significant linkage findings.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NHLBI)

The Coronary Artery Risk Development in Young Adults (CARDIA) Study: CARDIA is studying the distribution and evolution of risk factors for cardiovascular disease (CVD) during young adulthood in 5,115 African-American and white men and women who were aged 18-30 years when the study began in 1985. The project has completed 7 examinations of these participants over 20 years. CARDIA has measured standard CVD risk factors at all examinations to permit analyses of secular trends and interrelationships among risk factors. Measures of subclinical CVD, such as coronary artery calcium, carotid intima-media wall thickness, arterial compliance, and left ventricular mass and function also have been assessed. DNA will be analyzed to elucidate how genetic variability and gene-environment interactions may explain differences in the severity and progression of CVD. Major objectives for the upcoming eighth examination include identifying early adulthood antecedents and consequences of obesity, understanding the determinants and trajectories of CVD development in women during the menopausal transition, and further assessing the basis for racial differences in the development and progression of CVD.

- For more information, see <http://www.cardia.dopm.uab.edu>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NHLBI)

Genetic Epidemiology of COPD (COPDGene): This investigator-initiated research program is performing genetic testing in more than 10,000 current or former smokers to identify genes that are associated with the presence of COPD (chronic obstructive pulmonary disease). In this large and diverse cohort, half of the subjects will be women and one-third will be African American. Although COPD is the fourth most common cause of death in the United States, understanding why some smokers develop serious lung disease and others do not is lacking. Genetics studies may reveal factors that determine this differential susceptibility to disease. The COPDGene study will help to identify individuals at greatest risk, point to particular molecular pathways that may be involved in pathogenesis, and suggest possible targets for prevention and drug therapy. The phenotypic and genetic data generated by the program will be made available through an NIH data repository to allow additional research analyses by other investigators. COPDGene has thus far enrolled more than 4,000 subjects at 17 sites across the United States.

- This example also appears in Chapter 3: *Genomics*
- (E) (NHLBI)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition

through the age of risk. Investigators have identified several genes, including *GABRA2*, *ADH4*, *ADH5*, *CHRM2*, *GRM8*, *GABRR1*, and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
- For more information, see <http://zork.wustl.edu/niaaa>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
- (E) (NIAAA) (GPRA)

Unraveling the Complexity of the Genetics of Glaucoma: Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. It is the leading cause of blindness in African Americans. More than 2 million Americans have been diagnosed with glaucoma, and the prevalence of the disease will rise to a projected 3 million by 2020. Glaucoma research aims to understand the complex genetic factors that lead to common forms of the disease and to develop treatments that protect ganglion cells of the retina from the damage that leads to vision loss. Under GPRA, NIH set a goal by 2012 to identify the genes that control the risk of glaucoma. To achieve this goal, NIH launched a large genome-wide association study to identify glaucoma risk genes. NEIGHBOR (NEI Glaucoma Human Genetics CollaBORation) is a unique collaborative effort involving 22 investigators at 12 institutions throughout the United States. Approximately 2,000 cases and 2,000 age, sex, and ethnically matched controls will have their complete genome sequenced (genotyped) for a genome-wide association study to identify genetic variants associated with the disease. Genetic data and associated disease characteristics collected from NEIGHBOR will be made available to the research community through the NIH database of Genotypes and Phenotypes (dbGaP).

- Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):532-8. PMID: 15078671.
- For more information, see <http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html>
- This example also appears in Chapter 3: *Genomics*
- (E) (NEI, NLM) (GPRA)

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.

- Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
- For more information, see <http://www.searchfordiabetes.org/>
- For more information, see <http://www.todaystudy.org/index.cgi>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, CDC)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic widens, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining such topics as:

- Basic research on the physiology, psychology, and genetics of obesity in children.
 - Developing community-based partnerships to prevent and control childhood obesity.
 - Applying computational and statistical methodologies to design and analyze multilevel studies on childhood obesity. Multilevel studies include those that consider the range of biological, family, community, sociocultural, environmental, policy, and macro-level economic factors that influence diet and physical activity in children.
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-09-140.html>
 - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-023.html>
 - This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
 - (E/I) (NICHD, NCI, NHLBI, OBSSR)

Genetics of Diabetes: Diabetes is a common, potentially deadly and debilitating chronic disease that poses an enormous health care burden. Both of the most common forms of diabetes, type 1 and type 2, are caused by an intersection of genetic and environmental risk factors. Although genetic effects on developing diabetes are profound, they are not simple, as there are many genes that influence the likelihood of developing type 1 or type 2 diabetes. Further, ethnicity impacts both genetic and environmental risk factors. To learn more about diabetes genetics, particularly through new genomic technologies, NIH supports the Type 1 Diabetes Genetics Consortium to study type 1 diabetes, and several major grants to study the genetics of type 2 diabetes. These programs now have identified at least 40 genetic regions linked to type 1 diabetes and at least 38 type 2 diabetes genes. Other studies are refining our understanding of how these genes affect diabetes risk. Many of these projects are geared to collect data from multiple ethnic groups, but a recent initiative sought to advance knowledge of diabetes risk genes in specific racial and ethnic groups disproportionately affected by type 2 diabetes, to understand how different genes affect different populations.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html>
- For more information, see <http://www.t1dgc.org>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
- (E) (NIDDK, NHGRI, NIAID, NICHD)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

- For more information, see <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NIEHS, NCMHD)

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
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIAMS, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH) (GPRA)

Genetics of Chronic Kidney Disease: Researchers recently have made progress in uncovering the role of genetics in chronic kidney disease (CKD) arising from various causes. Scientists recently have identified a genetic region that is strongly associated with CKD in African Americans that arises as a consequence of conditions other than diabetes, such as high blood pressure and HIV-associated kidney disease. Several variants associated with the *MYH9* gene were identified as major contributors to excess risk of this kind of CKD among African Americans. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition is the underlying disorder. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to study progression of an inherited form of kidney disease, polycystic kidney disease (PKD). Phase I of the study demonstrated that magnetic resonance imaging accurately could track structural changes in the kidneys; Phase II showed that patients with mutations in the *PKD1* gene have more cysts and larger kidneys than patients with *PKD2* mutations. A planned third phase of CRISP will provide critical information about the validity of changes in kidney volume as a surrogate marker for loss of kidney function. NIH also has launched a study to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in patients with CKD, to predict risk, aid early diagnosis, and assess disease progression.

- Kopp JB, et al. *Nat Genet* 2008;40(10):1175-84. PMID: 18794856.
- Kao WHL, et al. *Nat Genet* 2008;40(10):1185-92. PMID: 18794854. PMID: PMC2614692.
- Grantham JJ, et al. *New Engl J Med* 2006;354(20):2122-30. PMID: 16707749.
- Rule AD, et al. *J Am Soc Nephrol* 2006;17(3):854-62. PMID: 16452494.
- For more information, see <http://www.nih.gov/news/health/sep2008/niddk-14.htm>
- For more information, see <http://www.nih.gov/news/pr/may2006/niddk-17.htm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
- (E/I) (NIDDK, AHRQ, NCI, NCCR, NHLBI)

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>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-09-176.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

Prevention of Diabetes in Women with a History of Gestational Diabetes: A past history of gestational diabetes mellitus (GDM) confers a very high risk of postpartum development of diabetes, particularly type 2 diabetes in women. This ancillary study of the Diabetes Prevention Program was a multicenter, randomized, controlled clinical trial of: 1) standard lifestyle/placebo, 2) standard lifestyle and metformin therapy, or 3) an intensive lifestyle intervention, and was conducted at 27 academic centers and Indian Health Services sites with a total of 2,190 women involved. The investigators found that in women with the same glucose levels at the beginning of the study, women with a history of GDM had a crude incidence rate of diabetes 71 percent higher than that of women without such a history. They also found that among women reporting a history of GDM, the reduction in the incidence of diabetes was approximately 50 percent for both the intensive lifestyle modification and metformin group compared with the placebo group. This ancillary study demonstrated that both intensive lifestyle and metformin are highly effective in delaying or preventing diabetes in women with a history of GDM.

- For more information, see <http://jcem.endojournals.org/cgi/content/full/93/12/4774>
- For more information, see <http://ndep.nih.gov/>
- For more information, see <http://diabetes.niddk.nih.gov/>
- (E) (ORWH, NIDDK)

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.

- For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NINR, NIA, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

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>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- (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.

- Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607.
PMCID: PMC2512256.
- Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDA)

The Rapid Response Program: In April 2002, NIH issued a major report on college drinking: *A Call to Action: Changing the Culture of Drinking at U.S. Colleges*. This report was developed by the NIH-supported Task Force on College Drinking, a group consisting of college presidents, researchers, students, and NIH staff. The report describes the magnitude of mortality and morbidity resulting from dangerous drinking behavior by college students and the consequences for both drinkers and nondrinkers. In addition, interventions found through rigorous research to reduce college drinking were reviewed. A copy of the report was mailed to every U.S. college president in 2002, as was the NIH report *What Colleges Need to Know Now: An Update on College Drinking Research in 2007*. In 2002-2003, NIH issued two RFAs: "Research Partnership Awards for Rapid Response to College Drinking Problems" and "Rapid Response to College Drinking Problems." From the applications in response to these RFAs, 5 investigators were matched with 15 colleges and universities to test a variety of individual, counseling, academic, policy, and community/campus partnership interventions to reduce college drinking, including residential learning communities, peer-facilitated alcohol interventions, peer-led motivational enhancement with freshmen women, freshmen parent-student initiatives, fraternity and sorority interventions, alcohol screening in a college health clinic, social norms programs, and a university assistance programs. Findings from these and some of NIH's 32 other grants examining college drinking prevention are available in a special June 2009 issue of the *Journal of Studies on Alcohol and Drugs*, which includes 15 articles related to this topic.

- Hingson RW, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):12-20. PMID: 19538908.
PMCID: PMC2701090.
- Faden VB, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):28-33. PMID: 19538910.
PMCID: PMC2701094.
- Schaus JF, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):131-141. PMID: 19538921.
PMCID: PMC2701092.
- Saltz RF, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):21-7. PMID: 19538909.
PMCID: PMC2701100.
- Amaro H, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):45-56. PMID: 19538912.
PMCID: PMC2701089.
- For more information, see <http://www.jsad.com/jsad/articles/Sup/16/260.html>
- (E) (NIAAA)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the

environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA-09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use"; and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

- A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: <http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm>. Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
- For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E, O) (NIAAA)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their Families:

Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

- For more information, see <http://www.drugabuse.gov/pdf/tib/veterans.pdf>
- This example also appears in Chapter 2: *Life Stages, Human Development, and*

- *Rehabilitation and Chapter 3: Epidemiological and Longitudinal Studies*
(E) (NIDA, NCI, NIAAA, NIMH)

Exercise Guide for Older Americans: In January 2009, NIH offered an update of its popular exercise guide, newly titled *Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging*. The guide is the result of a 2-year process overseen by the Task Force on Exercise and Physical Activity, which included top scientists conducting research on exercise and physical activity in older adults, as well as representatives from key organizations involved in promoting exercise and physical activity to the public, including CDC, the American College of Sports Medicine, and the International Council on Active Aging. Based on an intensive review by these experts of the evidence on physical activity, the updated publication reviews in lively, easy-to-understand language the benefits of physical activity for older people, discusses the importance of regular effort and goal setting, provides specific activities and exercises appropriate for varying strength and skill levels, and includes worksheets to help the reader track his or her progress. The new guide is proving popular already with the public; between 2000 and 2008, NIH distributed 1.2 million copies while in 2009, NIH has distributed more than 300,000 copies of the guide. NIH is undertaking an outreach effort on exercise, with the guide as a foundation, to encourage older people to become more physically active.

- For more information, see <http://www.nia.nih.gov/Exercise>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (O) (NIA)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

- Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
Centers for Disease Control and Prevention. Smoking-attributable mortality, years of

potential life lost, and productivity losses United States, 2000-2004. *Morb Mortal Wkly Rep* 2008;57(45):1226-28.

Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington, DC: National Academies Press; 2007.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html>
- For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDA, NCI) (GPRA)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

- For more information, see <http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm>
- For more information, see <http://nih.gov/news/health/dec2008/nhlbi-15.htm>
- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap/>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
- (E) (NHLBI, NLM)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

- For more information, see <http://www.genome.gov/27528559>
- For more information, see <http://www.genome.gov/27529231>
- For more information, see <http://www.genome.gov/27531390>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E, I) (NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH, NINDS)

Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy

(CALERIE): A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition can significantly lengthen life span. The CALERIE study will help to determine if these effects extend to humans. This long-term study began in January 2007 and is ongoing. Recently, CALERIE researchers used state-of-the-art techniques to measure metabolic changes that occur in response to caloric restriction with or without exercise. They found that energy metabolism slows in response to caloric restriction, but the addition of exercise to a caloric restriction regimen may forestall such a "metabolic adaptation," potentially explaining why a combination of dietary restriction and exercise, as opposed to dietary restriction alone, may be the best intervention to sustain weight loss. Overall, these findings provide important information about the mechanisms of weight loss and indicate that exercise may be an important component of a weight loss regimen.

- For more information, see <http://calerie.dcri.duke.edu>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA)

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 3: *Clinical and Translational Research*
- (I) (NIEHS)

Comorbidity of Depression with Other Chronic Diseases: Major depressive disorder is the leading cause of disability in the United States and affects approximately 14 million American adults

annually. Depression frequently occurs among individuals with other medical conditions, such as advanced heart disease, Parkinson's disease, and diabetes. Despite the increased risk of depression in the presence of other medical illnesses, comorbid depression is not typically recognized or adequately treated, particularly over the course of chronic illnesses. NIH is undertaking multiple strategies to guide efforts at reducing the years lost to disability as a result of comorbid depression. A GPRA goal was developed to synchronize research efforts focused on early detection, prevention, and treatment of depressive disorders, and their relationship to other chronic diseases. The quality of care available to persons with treatment-resistant depression, as well as treatment for persons with depression that is comorbid with other medical illnesses, will improve as (1) knowledge of the causes and processes of depression expands, including the genetic, environmental, behavioral, and cultural risk and protective factors; (2) psychosocial and pharmacological treatments become more refined and targeted; and (3) strategies are developed for protecting individuals from relapse and recurrence of depression.

- (E/I) (NIMH) (GPRA)

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>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0029.html>
- For more information, see <http://www.nida.nih.gov/ResearchReports/comorbidity>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDA, NIAAA, NIMH)

Advances in Understanding the Genomic Risk for Schizophrenia: Three genome-wide studies have pinpointed a vast array of genetic variation that cumulatively poses the greatest risk for

schizophrenia yet reported. All three studies implicate an area of chromosome 6 (6p22.1), which is known to harbor genes involved in immunity and genes that control how and when genes turn on and off. Among sites showing the strongest associations with schizophrenia was a suspect area on chromosome 22 and more than 450 variations in the suspect area on chromosome 6. Individually, these variants' effects statistically were insignificant, but cumulatively they were very powerful. Additionally, one of the studies traced schizophrenia and bipolar disorder, in part, to the same chromosomal neighborhoods. These findings suggest that if some of the same genetic risks underlie schizophrenia and bipolar disorder, then these disorders may originate from a common vulnerability in brain development.

- Shi J, et al. *Nature* 2009;460(7256):753-7. PMID: 19571809. PMCID: PMC2775422.
- Stefansson H, et al. *Nature* 2009;460(7256):744-7. PMID: 19571808.
- International Schizophrenia Consortium, et al. *Nature* 2009;460(7256):748-52. PMID: 19571811.
- This example also appears in Chapter 3: *Genomics*
- (E) (NIMH)

Vitamin D Initiative: Vitamin D is an essential nutrient for maintaining health. In addition to enhancing calcium metabolism, accumulating evidence indicates that vitamin D may play other roles in human health, including supporting immune function; reducing inflammation; and supporting cell proliferation, differentiation, and programmed cell death. The importance of vitamin D to health has stimulated new research, resulting in growing concerns about the sufficiency of vitamin D levels in the U.S. population. To address these issues, NIH has established the Vitamin D Federal Working Group, which is translating the research needs in this area into actions by appropriate Federal research groups. The National Institute of Standards and Technology developed standard reference materials for vitamin D to facilitate analyses of vitamin D in foods and human fluids. The data on vitamin D collected through the National Health and Nutrition Examination Survey are being analyzed for trends in the nutritional status of the public. The NIH ICs are collaborating by providing funding opportunities to support research that will close the gaps in knowledge. NIH also expects that these vitamin D-related activities will inform the reappraisal by the Food and Nutrition Board of the Institute of Medicine of the dietary recommendations for vitamin D and calcium.

- (E) (ODP/ODS)

Treating Chronic Disease and Comorbidities

Patient-Reported Outcomes Measurement Information System (PROMIS): The PROMIS initiative is developing new ways to measure patient-reported outcomes (PROs) for clinical research, such as pain, fatigue, physical functioning, emotional distress, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases. The first phase of PROMIS successfully has addressed its initial broad objectives of developing and testing a large item (survey question) bank for measuring PROs, along with translation of certain items into Spanish; creating a computer adaptive testing (CAT) system that allows for efficient, scientifically robust assessment of PROs in patients with a spectrum of chronic diseases; and producing a publicly available, Web-based system that continues to be updated and modified, to allow clinical researchers access to PROMIS resources, such as a common repository of validated items, a CAT system, and hard copy surveys. Preliminary results demonstrate that a short, 10-item PROMIS survey, administered by CAT, outperforms the most commonly used, paper-based, self-reporting assessment

tool for arthritis disability (the Health Assessment Questionnaire). These results are indicative of the anticipated advantages of the PROMIS tool: better answers with fewer patients. The success of the project has garnered 4 more years of NIH funding for PROMIS. Prioritized tasks for PROMIS include validating and evaluating usability in future NIH-supported clinical trials, including Spanish translations; developing additional modes of administration; facilitating adoption of PROMIS by the clinical research community; and building partnerships to secure long-term sustainability for the PROMIS tools.

- For more information, see <http://nihroadmap.nih.gov/clinicalresearch/overview-dynamicoutcomes.asp>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIAMS, Common Fund - all ICs participate)

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: Clinical and Translational Research
 - (E/I) (NIAAA) (GPRA)

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 3: Clinical and Translational Research
- (E) (NIDA) (GPRA)

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.

- Kobayashi YM, et al. *Nature* 2008;456(7221):511-5. PMID: 18953332. PMID: PMC2588643.
- Narkar VA, et al. *Cell* 2008;134(3):405-15. PMID: 18674809. PMID: PMC2706130.
- O'Connor RS, et al. *J Physiol* 2008;586(Pt 12):2841-53. PMID: 18420707. PMID: PMC2517193.
- 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
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIAMS, NCCR, NIA, NICHD, NINDS) (COE)

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.

- Du M, et al. *Proc Natl Acad Sci U S A* 2008;105(6):2064-9. PMID: 18272502. PMCID: PMC2538881.
- Galletta LJV, et al. *FEBS Letters* 2001;499(3):220-4. PMID: 11423120.
- For more information, see <http://www2.niddk.nih.gov/Research/ScientificAreas/GeneticGeneTherapy/GCTR.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK)

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 3: Clinical and Translational Research
- (I) (NIA)

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>
- For more information, see <https://rarediseases.info.nih.gov/TRND/>
- This example also appears in Chapter 3: *Clinical and Translational Research* (E/I) (ODP/ORDR, NHGRI)

Long-Term Oxygen Treatment Trial (LOTT): Although oxygen therapy is known to benefit patients who have chronic obstructive pulmonary disease (COPD) and experience severe hypoxemia when resting, its value for patients with less-serious disease is not known. In November 2006, NIH and the Centers for Medicare and Medicaid Services launched the LOTT, the largest-ever randomized clinical trial of the effectiveness and safety of long-term, home oxygen therapy for patients with COPD and moderately severe hypoxemia. Results are expected to shed light on the role of oxygen therapy in the management of such patients and provide a scientific basis for Medicare coverage decisions. The LOTT trial is the focus of a new GPRA goal—"By 2012, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia."

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-11-20.htm>
- (E) (NHLBI) (GPRA)

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 3: *Clinical and Translational Research*

- (E) (NHLBI)

Idiopathic Pulmonary Fibrosis Clinical Research Network: The idiopathic pulmonary fibrosis (IPF) clinical research network was established in 2005 to explore treatment of patients with newly diagnosed IPF using combinations of drugs at multiple points that could stabilize or improve the disease. The network includes 11 clinical centers (with multiple satellite sites), a data coordinating center, and a clinical research skills-development core. The first clinical trial to treat pulmonary hypertension in patients with advanced IPF was completed in September 2009, and preliminary results are expected by November 2009. Two additional protocols are to begin in fall 2009. One will test the results of a prior trial that treated IPF patients with a combination of corticosteroids, azathioprine, and n-acetylcysteine (NAC) by using a multiple-arm, double-blind, randomized trial to ascertain if the findings were the effect of NAC only. A second trial will assess the effect of oral anticoagulation therapy on the progression of fibrosis in IPF patients. Additionally, the network has enabled support of a number of new ancillary mechanistic studies that are conducted in conjunction with the main intervention trials.

- For more information, see <http://www.ipfnet.org>
- (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 disturbs 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.

- Kushida CA, et al. *J Clin Sleep Med* 2006;2(3):288-300. PMID: 17561541.
- Saboisky JP, *Expert Opin Ther Targets* 2009;13(7):795-809. PMID: 19530985. PMID: PMC2729816.
- Calvin AD, et al. *Metab Syndr Relat Disord.* 2009;7(4):271-8. PMID: 19344228.
- For more information, see <https://apples.stanford.edu>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI)

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 fibrates 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.

- Action to Control Cardiovascular Risk in Diabetes Study Group, et al. *N Engl J Med* 2008;358(24):2545-59. PMID: 18539917.
- For more information, see <http://clinicaltrials.gov/ct2/show/>
- For more information, see <http://www.accordtrial.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI, CDC, NEI, NIA, NIDDK)

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.

- Diabetic Retinopathy Clinical Research Network, et al. *Ophthalmology* 2007;114(10):1860-7. PMID: 17698196. PMCID: PMC2245885.
- For more information, see <http://public.drcre.net/>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

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.

- Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. 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: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

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: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly 600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10 to 13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is

continuing as the participating children go through adolescence and enter adulthood.

- Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0028.html>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0029.html>
- For more information, see <http://www.nida.nih.gov/ResearchReports/comorbidity/>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDA, 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>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00765895>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00248651>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00738920>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00688662>
- For more information, see <http://www.cns.med.ucla.edu>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, NCCAM, ORWH)

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.

- Szeffler SJ, et al. *Lancet* 2008;372(9643):1065-72. PMID: 18805335. PMCID: PMC2610850.
- For more information, see <http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E) (NIAID)

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.

- Lee WM, et al. *Gastroenterology* 2009;137(3):856-64, 864.e1. PMID: 19524577.
- For more information, see <http://www.jhucct.com/nash/>
- For more information, see <http://diln.dcri.duke.edu/>
- For more information, see <http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html>
- For more information, see <http://www.palfstudy.org/>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, FDA, NCI, NICHD) (GPRA)

Pelvic Floor Disorders: Research supported by NIH showed that nearly one-quarter of all U.S. women were afflicted with one or more pelvic floor disorders. These disorders result when the muscles and connective tissue within the pelvic cavity weaken or are injured, leading to dysfunction of one or more pelvic organs. The NIH-supported Pelvic Floor Disorders Network, with seven sites throughout the country, supports research on the prevention and treatment of pelvic floor disorders. A recent study by the network revealed that a special two-step surgical procedure, compared to

standard practice, reduced by half the incidence of urinary incontinence in women with pelvic organ prolapse. In addition, NIH plans to enhance collaborative research among basic scientists and clinician researchers in female pelvic floor disorders, to promote research that has the greatest clinical applicability for addressing unknown aspects of physiology and pathophysiology of pelvic function.

- For more information, see <http://www.pfdnetwork.org/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-008.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NICHD, NIDDK, ORWH)

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.

- Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
- Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
- For more information, see <http://www.uitn.net/>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, NICHD)

Chemical Messengers in the Brain Determine the Response to Stress and Regulate Craving For Alcohol: Stress contributes to many disease states, including alcohol dependence. As alcohol dependence evolves, stress systems in the brain play an increasing role in continued alcohol use and relapse. Furthermore, individuals differ widely in response to stress. NIH researchers have investigated specific chemical messengers in the brain and the roles these messengers play as mediators of behavioral stress responses and their contributions to alcohol dependence. For example, the chemical messenger neuropeptide Y (NPY) is expressed in regions of the brain implicated in arousal and in determining emotional states. Production of NPY increases in these brain regions in response to emotionally charged and stressful conditions. Higher levels of NPY are associated with lower levels of alcohol consumption. NIH researchers also have made progress in studies of another brain messenger involved in stress responses, Neurokinin 1 (NK1) and its receptor

(NK1R). In a clinical study, alcohol-dependent inpatients who recently stopped drinking were treated with a drug that blocks the actions of NK1R. Patients treated with the NK1R blocker exhibited reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. Brain imaging during responses to stimulation that increases the likelihood of drinking showed a beneficial effect by the drug, suggesting that such drugs could reduce relapse in alcohol-dependent individuals.

- Zhou Z, et al. *Nature* 2008;452(7190):997-1001. PMID: 18385673. PMID: PMC2715959.
- George DT, et al. *Science* 2008; 319(5869):1536-9. PMID: 18276852.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIAAA)

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.

- Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
- The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
- 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>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIDDK, ORWH)

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.

- DeRouen TA, et al. *J Am Dent Assoc* 2008;139(3):339-45. PMID: 18310739.
- Gilbert GH, et al. *J Am Dent Assoc* 2008;139(1):74-81. PMID: 18167389.
- For more information, see <http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDCR)

End-Stage Renal Disease: According to the United States Renal Data System—an NIH-supported national data system that collects, analyzes, and distributes information about people with kidney failure—more than one-half million Americans suffer from kidney failure. Patients with this condition—known as end-stage renal disease or ESRD—require a kidney transplant or hemodialysis, a process that uses a machine to remove waste products and excess fluid from the bloodstream. To facilitate hemodialysis, some patients undergo a surgical procedure to create a site on the body that allows easy, repeated access to the blood vessels. However, over time, many vascular access sites become unusable and fail. The NIH-supported Dialysis Access Consortium found that treatment with an anti-blood clotting drug did not improve the long-term suitability of a type of access known as a fistula. A separate study by the consortium found that the long-term usability of a different type of access site, known as a graft, could be improved through treatment with a combination of aspirin and another anti-clotting drug. Still, important questions remain. To better understand the underlying biology of access site maturation, NIH is launching a Vascular Biology of Hemodialysis Vascular Access Consortium to study the molecular and cellular pathways that contribute to vascular injury and high rates of vascular access failure. Such research may inform new strategies to improve outcomes in patients undergoing hemodialysis.

- Dember LM, et al. *JAMA* 2008;299(18):2164-71. PMID: 18477783.
- Dixon BS, et al. *New Engl J Med* 2009;360(21):2191-201. PMID: 19458364.
- For more information, see <http://www.usrds.org>
- For more information, see <http://www.nih.gov/news/health/may2008/niddk-22a.htm>
- For more information, see <http://www.nih.gov/news/health/may2009/niddk-20.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDDK)

Using the Web to Broaden the Delivery of Effective Treatments: NIH is testing the efficacy of delivering evidence-based psychosocial interventions for drug abuse and HIV prevention via the Web or other computer-based media, while assessing their relative cost and efficacy compared to more traditional delivery formats. Variables of interest include abstinence, treatment retention, health risk, quality of life, and social outcomes. New research shows that computer-based training for cognitive behavioral therapy appears to have both short-term and enduring effects on drug use—that is, fewer days of drug use for many months following treatment compared to controls. Another computer-based intervention, called Positive Choice, was tested in HIV-positive patients as a means of reducing risky behaviors that lead to HIV spread. Five San Francisco clinics participated, exposing patients to a

"video doctor" to conduct a risk assessment and risk reduction counseling program. Patients waiting to see the provider use a laptop computer to watch video clips and respond by means of a color-coded keyboard. That, too, was successful, and sharply reduced sexual and drug risk behaviors in HIV-positive patients. These delivery methods stand not only to greatly increase cost effectiveness of interventions, but to provide a means for broader dissemination, including to those in remote locations where therapists may not be available. Our research will continue to investigate how such interactive technology can be integrated to improve the addiction treatment system and bring about more widespread adoption of evidence-based approaches.

- For more information, see <http://ajp.psychiatryonline.org/cgi/content/full/165/7/>
- For more information, see <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001988>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIDA)

Asthma Exacerbations: In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control asthma symptoms. Twelve projects have been funded under this initiative. NIH is assessing the progress of the initiative through an ongoing GPRA goal—"to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014."

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NHLBI) (GPRA)

Acute Kidney Injury: Acute kidney injury (also called "acute renal failure") is a serious medical condition characterized by a relatively rapid loss of kidney function, resulting in an inability to excrete waste products and excess fluid and salts. It is a common complication in hospitalized patients, and mortality rates approach 50 percent among the critically ill. There is no effective drug treatment, so physicians rely on hemodialysis and other forms of life-sustaining kidney replacement therapy. Some earlier, small studies suggested that increased frequency or intensity of hemodialysis might improve survival in patients with acute kidney injury. The NIH-funded Acute Renal Failure Trial Network (ATN) Study enrolled more than 1,100 critically ill patients with acute kidney injury as well as failure of at least one additional organ or a serious infection (sepsis). It found no significant difference in death rates after 60 days between patients treated with conventional dialysis and those who received a more intensive dialysis regimen. These findings may spare patients from unnecessarily intensive medical interventions, and also underscore the need for research into other approaches to treating acute kidney injury. NIH recently launched a Natural History of Acute Kidney Injury study—ASSESS AKI—to identify and validate biomarkers and risk assessment tools for kidney function, injury, and recovery in patients with acute kidney injury; a subset of this study will focus on pediatric patients.

- The VA/NIH Acute Renal Failure Trial Network, et al. *New Engl J Med* 2008;359(1):7-20. PMID: 18492867. PMCID: 2574780.
- For more information, see <http://www.nih.gov/news/health/may2008/niddk-22.htm>
- (E) (NIDDK)

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.

- For more information, see <http://www.nei.nih.gov/news/pressreleases/022208.asp>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

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.

- BARI 2D Study Group, et al. *N Engl J Med* 2009;360(24):2503-15. PMID: 19502645.
- For more information, see <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?>
- For more information, see <http://content.nejm.org/cgi/reprint/360/24/2503.pdf>
- For more information, see <http://content.nejm.org/cgi/reprint/360/24/2570.pdf>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI, NIDDK)

Improving Transplantation Outcomes: Organ transplantation prolongs survival and greatly improves quality of life for children and adults suffering from a wide range of congenital and acquired diseases. Yet, despite advances in transplantation, normal life expectancy and health-related quality of life are not restored fully by organ transplantation. To improve the outcomes of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies.

In one notable CTOT study, NIH-supported investigators developed a regimen that included transplantation of both kidney and bone marrow from the same donor and use of immunosuppressive

therapies prior to and just after transplantation. Nine to 14 months after the transplant, investigators were able to discontinue all immunosuppressive medications with this regimen in four of the five patients, without subsequent rejection of the kidney. In another study, NIH-supported investigators studied whether acute graft rejection was associated with changes in the expression of genes involved with the adaptive immune response. They measured levels of microRNAs in healthy transplanted kidneys and in transplants undergoing rejection. The team found a pattern of six microRNAs that could distinguish healthy kidneys from those in the process of being rejected. These results suggest that microRNAs may be a useful measurement for assessing human kidney transplant status. If the rejection signature appears early enough, doctors one day may be able to treat patients before organ damage occurs and to better tailor immunosuppressive therapy to the individual patient.

- Kawai T, et al. *N Engl J Med* 2008 Jan 24;358(4):353-61. PMID: 18216355. PMCID: PMC2819046.
- For more information, see <http://www.immunetolerance.org/>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* (E) (NIAID, NHLBI, NIDDK)

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/>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
- (E) (NIAID, NIDDK)

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.

- Cornea Donor Study Investigator Group, et al. *Ophthalmology* 2008;115(4):620-626.e6. PMID: 18387407.
- For more information, see <http://www.ophsource.org/periodicals/ophtha/article/PIIS0161642008000055/fulltext>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine:

In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences. According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

- Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
- For more information, see <http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NCCAM, CDC)

Glucosamine and Chondroitin Fare No Better Than Placebo in Slowing Structural Damage of Knee Osteoarthritis:

Osteoarthritis affects an estimated 27 million Americans, and researchers are seeking ways not only to treat pain, but also to address the loss of cartilage—a hallmark of the condition. The two-part Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), funded by NIH, investigated whether this dietary supplement can treat pain and diminish structural damage

associated with knee osteoarthritis. In the primary study (GAIT I), combined glucosamine/chondroitin sulfate did not provide significant relief among study participants overall, although a smaller subgroup with moderate to severe pain did show significant relief. The 18-month GAIT II ancillary study followed cartilage loss in GAIT participants with moderate or severe osteoarthritis in one or both knees, comparing the effects of glucosamine and/or chondroitin sulfate with placebo. In GAIT II, glucosamine and chondroitin—together or alone—appeared to fare no better than a placebo in slowing loss of cartilage in osteoarthritis of the knee, measured by joint space width as seen on x-rays. Interpreting the study results is complicated, however, because participants taking placebo had a smaller loss of cartilage than predicted. In addition to its findings on the effects of dietary supplements taken by many Americans for osteoarthritis, GAIT II provided new insights on osteoarthritis progression, techniques for measuring loss of joint space width, and characteristics of osteoarthritis patients who may respond best to glucosamine/chondroitin.

- Sawitzke AD, et al. *Arthritis Rheum* 2008;58(10):3183-91. PMID: 18821708.
- For more information, see <http://nccam.nih.gov/news/2008/092908.htm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NCCAM, NIAMS)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

- Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/102408.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NCCAM)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a

cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

- This example also appears in Chapter 2: Life Stages, Human Development, and Rehabilitation and Chapter 3: Epidemiological and Longitudinal Studies
- (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.
 - Salvatore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
 - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html>
 - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html>
 - This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
 - (E/I) (NIMH)

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>
- For more information, see <http://www.clinicaltrials.gov/show/NCT00590863>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIMH)

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 3: *Clinical and Translational Research*
- (E) (NIMH) (ARRA)

Addressing Pain and Palliative Care in Chronic Diseases

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New

Targets for Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which

stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

- Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing, and then controlling, images of their own brains in real time.

- Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
- Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.
- Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.
- Ledebner A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.
- deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDA, NINDS)

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 discectomy is a cost-effective treatment, regardless of whether the damaged disk is in the upper or lower portion of the lumbar spine.

- Lurie JD, et al. *J Bone Joint Surg Am* 2008;90(9):1811-9. PMID: 18762639. PMCID: PMC2657310.
- Tosteson AN, et al. *Ann Intern Med* 2008;149(12):845-53. PMID: 19075203. PMCID: PMC2658642.
- Tosteson AN, et al. *Spine* 2008;33(19):2108-15. PMID: 18777603.
- Weinstein JN, et al. *Spine* 2008;33(25):2789-800. PMID: 19018250. PMCID: PMC2756172.
- Weinstein JN, et al. *N Engl J Med* 2007;356(22):2257-70. PMID: 17538085. PMCID: PMC2553804.
- Weinstein JN, et al. *N Engl J Med* 2008;358(8):794-810. PMID: 18287602. PMCID: PMC2576513.
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIAMS, CDC/NIOSH, ORWH)

Acupuncture-Like Treatments Improve Outcomes Compared With Usual Care for Low-Back Pain:

Chronic low-back pain is a common condition that can be difficult to treat. In a recent NIH-funded clinical trial, researchers at the Group Health Center for Health Studies in Seattle compared the efficacy of acupuncture, simulated acupuncture, and conventional care for chronic low-back pain. In the trial, 638 adults with chronic low-back pain were randomly assigned to 1 of 4 groups: individualized acupuncture, involving a diagnostician's customized prescription for needle placement; standardized acupuncture, using a single prescription for acupuncture points that experts consider generally effective for chronic low-back pain; simulated acupuncture, which mimics needle acupuncture without actual penetration of the skin; or usual care, which is standard medical care. At 8 weeks, all 3 acupuncture groups improved their dysfunction scores significantly more than the group receiving usual care. However, there was no significant difference between the groups receiving the actual and simulated acupuncture. Neither tailoring acupuncture needle sites to an individual patient nor penetrating the skin appears to be important for receiving therapeutic benefit. Although the researchers were encouraged that acupuncture-like treatments appear to be helpful for people suffering from low-back pain, the finding that actual acupuncture produced no greater benefit than simulated acupuncture raises important questions about acupuncture's mechanisms of action. The researchers recommend further research to determine the roles of patient expectancy, practitioner

reassurance, and the physiological effects of noninsertive stimulation and other effects that may contribute to acupuncture-like benefits.

- Cherkin DC, et al. *Arch Intern Med* 2009;169(9):858-66. PMID: 19433697.
- For more information, see <http://nccam.nih.gov/news/2009/051109.htm>
- (E) (NCCAM)

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>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI, NINDS)

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.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (NINR, NCI)

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.

- For more information, see <http://officeofbudget.od.nih.gov/br.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NINR, NCI) (GPRA)

A Commitment to Global Health

A Nationally Representative Case-Control Study of Smoking and Death in

India: Background: Recent evidence suggests that there are 120 million smokers in India. While smoking is registering a steady decline in western countries, experts estimate that it is increasing in India. Despite the magnitude of the smoking epidemic in India, there are no reliable studies that have assessed the effects of prolonged smoking of cigarettes or "bidis" on mortality. Advance: This is the first nationwide study conducted to assess the hazards of smoking among men and women in India. About 1.1 million homes in India were surveyed from 2001-2003. Researchers compared the smoking histories of 74,000 adults who had died during the study period against 78,000 unmatched controls. The study found that more than 30 percent of men and 5 percent of women aged 30-60 years smoked regular cigarettes or bidis. Smoking was associated with a 6- and 8-year reduction in median survival for men and women, respectively. The study confirmed that there are no safe levels of smoking. Significance: The results of this landmark study were published in several Indian newspapers in February 2008, thereby informing the public and policy makers on the impact of smoking in India. In response to this study, the Indian Health Minister said that "The Government of India is trying to take all steps to control tobacco use—in particular by informing the poor and the illiterate." This science advance supported by NIH's International Tobacco and Health Research and Capacity Building Program provides important evidence on the smoking epidemic in India and lays the foundation on which tougher smoking standards can be enforced.

- Jha P, et al. *N Engl J Med* 2008;358(11):1137-47. PMID: 18272886.
- For more information, see <http://www.hindu.com/2008/02/14/stories/2008021455551300.htm>
- For more information, see <http://content.nejm.org/cgi/content/full/358/11/1137>
- For more information, see http://www.fic.nih.gov/programs/research_grants/tobacco/
- (E) (FIC, NCI)

Global Health Initiative in Cardiovascular and Lung Diseases: In June 2009, NIH joined the United Health Chronic Disease Initiative and established a network of 11 Collaborating Centers of Excellence in low- and middle-income countries to build sustainable programs to combat chronic cardiovascular and lung diseases. The Centers are developing infrastructures for research and training to enhance their capacity to conduct population-based clinical research to monitor, prevent, or control

chronic diseases. Each Center pairs a research institution in a developing country with at least one academic institution in a developed country. Nine of the 11 main developed country partners are institutions located in the United States. The program is expected to stimulate clinical, epidemiological, behavioral, and translational research, as well as research on health services, treatment outcomes, and health policy.

- Nabel EG, et al. *Lancet* 2009;373(9680):2004-6. PMID: 19523681.
- Daar AS, et al. *Nature* 2007;450(7169):494-6. PMID: 18033288.
- For more information, see <http://www.nhlbi.nih.gov/about/globalhealth/index.htm>
- (E) (NHLBI)

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 new 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.

- For more information, see <http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx>
- For more information, see <http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (O) (FIC, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Millennium Promise Awards: World Health Organization (WHO) statistics show that about 60 percent of all deaths worldwide are attributable to chronic diseases, and 80 percent of them occur in low- and middle-income countries (LMICs). To address the significant and growing burden of chronic disease in LMICs, in July 2008, NIH launched a \$1.5 million-a-year grant program, Millennium Promise

Awards: Noncommunicable Chronic Diseases Research Training Program to support the training of researchers to fight chronic diseases in LMICs. This research training program is designed to build research capacity in LMICs in fields related to cancer; cerebrovascular disease including stroke; lung disease including chronic obstructive pulmonary disease and environmental factors including indoor air pollution; obesity and lifestyle factors related to these conditions; and genetics of noncommunicable diseases. The objectives of the program are to train a cadre of experts in LMICs who can assess the magnitude of chronic diseases in LMICs; address chronic diseases in a culturally relevant and sensitive manner; develop methods to monitor and understand the causes of chronic disease; work in chronic diseases across a broad range of research areas from genetics to implementation science; and translate research into public health policy and programs.

- For more information, see http://www.fic.nih.gov/programs/training_grants/ncod/index.htm
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-175.html>
- (E) (FIC, NCI, NICHD, NIEHS, NINDS, NINR, ODP/ODS)

NIH Strategic Plans Pertaining to Chronic Diseases and Organ Systems

National Heart Lung and Blood Institute (NHLBI)

- [*NHLBI Strategic Plan: Shaping the Future of Research*](#)

National Cancer Institute (NCI)

- [*NCI Strategic Plan for Leading the Nation*](#)

National Institute of Dental and Craniofacial Research (NIDCR)

- [*NIDCR Strategic Plan*](#)
- [*NIDCR Implementation Plan*](#)

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

Strategic Plans:

- [*National Diabetes Education Program \(NDEP\) Strategic Plan*](#)
- [*Overcoming Bladder Disease—A Strategic Plan for Research*](#)
- [*Renal Disease Research Plan*](#)
- [*Strategic Plan for Polycystic Kidney Disease*](#)
- [*Strategic Plan of the National Kidney Disease Education Program \(NKDEP\)*](#)
- [*Strategic Plan for Pediatric Urology: The Strategic Plan for Pediatric Urology, NIDDK—Research Progress Report*](#)
- [*NIDDK Prostate Research Strategic Plan*](#)

Reports from Planning Activities:

- [*Clinical Research on Kidney Disease*](#)
- [*NIDDK Annual Compendium of Recent Advances and Emerging Opportunities*](#)

- [Progress Report on NIDDK Efforts to Promote Translational Research](#)
- [Research Needs in Pediatric Kidney Disease—2000 and Beyond](#)
- [Strategic Planning for Polycystic Kidney Disease](#)
- [Urolithiasis Research Symposium](#)

National Institute of Allergy and Infectious Diseases (NIAID)

- NIH Autoimmune Diseases Coordinating Committee: *Progress in Autoimmune Diseases Research (2005)*
- [Report of the Expert Panel on Food Allergy Research \(2006\)](#)
- [NIH Action Plan for Transplantation Research \(2007\)](#)

National Eye Institute (NEI)

- [National Eye Institute Strategic Planning](#)
- [National Plan for Eye and Vision Research \(2004\)](#)
- [Progress in Eye and Vision Research 1999-2006](#)
- [Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation \(2007\)](#)
- [Age-Related Macular Degeneration Phenotype Consensus Meeting Report](#)
- [Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report](#)
- [Report of the Advances in Optical Imaging Symposium](#)

National Institute on Aging (NIA)

- [Living Long and Well in the 21st Century: Strategic Directions for Research on Aging](#)

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

- [NIAMS Long-Range Plan: Fiscal Years 2006-2009](#)
- [NIAMS Long-Range Plan: Fiscal Years 2010-2014](#)

National Institute of Mental Health (NIMH)

- [The National Institute of Mental Health Strategic Plan](#)

National Institute on Drug Abuse (NIDA)

- [NIDA Five-Year Strategic Plan 2009](#)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- [National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY08-13](#)

Recommendations of the NIAAA Extramural Advisory Board (EAB):

- [Developing an NIAAA Plan for HIV-Related Biomedical Research](#)
- [Fetal Alcohol Spectrum Disorders Research](#)
- [Mechanisms of Alcohol Addiction](#)
- [Mechanisms of Behavioral Change](#)

- [Gut-Liver-Brain Interactions in Alcohol-Induced Pathogenesis](#)
- [Mechanisms of Alcohol Action and Injury](#)
- [Medications Development](#)

National Institute of Nursing Research (NINR)

- [NINR Strategic Plan: Changing Practice, Changing Lives](#)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- [Contraception and Reproductive Health Branch \(CRHB\), NICHD, Report to the NACHHD Council, June 2008](#)
- [Endocrinology, Nutrition, and Growth \(ENG\) Branch Report to Council](#)

National Center for Complementary and Alternative Medicine (NCCAM)

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

John E. Fogarty International Center (FIC)

- [Pathways to Global Health Research: Strategic Plan 2008-2012](#)

Office of AIDS Research (OAR)

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)
- [FY 2009 Trans-NIH Plan for HIV-Related Research](#)
- [FY 2010 Trans-NIH Plan for HIV-Related Research](#)

Office of Dietary Supplements (ODS)

- [Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009](#)

Trans-NIH Strategic Plans

- [Strategic Plan for NIH Obesity Research](#)
(CSR, DNRC, FIC, NCCAM, NCI, NCMHD, NCR, NHGRI, **NHLBI**, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCR, **NIDDK**, NIEHS, NIMH, NINDS, NINR, OBSSR, ODP, ODS, ORWH, OSP)
- [Action Plan for Liver Disease Research](#)
(CSR, FIC, NCCAM, NCI, NCR, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCR, **NIDDK**, NIEHS, NIGMS, NINDS, NINR, NLM)
- [NIH Action Plan for Transplantation Research \(2007\)](#)
(NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)
- [Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases](#)
(NINR, ORWH, NIA, NICHD, **NIDDK**, NIBIB, NIDA, NCCAM, NIEHS, NCI, NIGMS, NIAID, NCMHD, NIAAA)

Detailed Burden of Illness and Related Health Statistics¹¹²

Although a comprehensive listing of burden estimates for all chronic diseases is not feasible within the format of this document, the following summary illustrates the depth and breadth of the chronic disease burden:

<p>Cardiovascular Diseases¹¹³</p>	<p>Coronary heart disease Mortality: 446,000 (2005) Prevalence: 16.8 million (2006)</p> <p>Heart failure Mortality: 57,000 (2004) Prevalence: 5.7 million (2006)</p> <p>Arrhythmias Prevalence: > 2 million with atrial fibrillation</p> <p>Congenital heart defects Incidence: 8 of every 1,000 newborns (35,000 per year) Prevalence: 1 million adults</p> <p>Peripheral arterial disease Prevalence: 8-12 million</p>
<p>Lung Diseases¹¹⁴</p>	<p>Chronic obstructive pulmonary disease Mortality: 127,000 (2005) Prevalence: 12 million people diagnosed; additional 12 million undiagnosed (2006)</p> <p>Asthma Mortality: 4,000 (2005) Prevalence: 23 million (2006) Total costs (direct and indirect): \$19.7 billion (2007)</p> <p>Cystic Fibrosis Prevalence: 30,000 Incidence: 1,000 new cases per year</p>
<p>Diabetes Mellitus¹¹⁵</p>	<p>Mortality: 233,619 (2005); 7th leading cause of death Prevalence: 23.6 million (diagnosed and undiagnosed); type 1 diabetes accounts for 5-10% of diagnosed cases (2007) Total costs (direct and indirect): \$174 billion (2007)</p>
<p>Obesity¹¹⁶</p>	<p>Prevalence: 34.6% of adults are overweight; 31.4% of adults are obese; 17.1% of children (aged 6-11) and 17% of adolescents (aged 12-19) are overweight (2006) Total health care costs (direct and indirect): \$117 billion (2002)</p>
<p>Chronic Kidney Disease¹¹⁷</p>	<p>Prevalence: 11.5% of adults age 20 or older (23.2 million people) (1999-2000) Costs: \$33.6 billion in public and private spending for treating end-stage</p>

	renal disease (ESRD) (2006)
Urologic Diseases ¹¹⁸	<p><i>Benign prostatic hyperplasia</i> Prevalence: 6.5 million Caucasian men aged 50-79 (2000) Cost (direct): \$1.1 billion (2000)</p> <p><i>Painful bladder syndrome/interstitial cystitis</i> Prevalence: 0.8% of women (1.2 million) and 0.1% of men (0.08 million) (1988-1994) Cost (direct): \$65.9 million (2000)</p> <p><i>Kidney stones</i> Prevalence: 5% of adults (1988-1994) Cost: \$2.07 billion (2000)</p> <p><i>Urinary incontinence</i> Prevalence: 38% of women and 17% of men, aged 60 and older (1999-2000) Cost (direct): \$463.1 million</p> <p><i>Urinary tract infection</i> Prevalence: 13% of women (12.8 million) and 2.3% of men (2 million) had a UTI in the last 12 months (1994) Cost (direct): \$3.5 billion (2000)</p>
Digestive Diseases ¹¹⁹	<p>Mortality: 236,000 (2004) Prevalence: 60-70 million people (1996) Disability: 1.9 million people unable to perform daily activities (1990-1992) Costs: \$97.8 billion (direct); \$44 billion (indirect) (2004)</p>
Chronic Liver Disease ¹²⁰	<p><i>Chronic liver disease or cirrhosis</i> Mortality: 27,013; 12th leading cause of death (2004) Prevalence: 5.5 million people (2-3% of adults) (1998) Cost (direct and indirect): \$1.6 billion (1998)</p> <p><i>Gallbladder disease</i> Mortality: 3,086 (2004) Prevalence: 12% of adults (20 million) (1998) Cost: \$6.4 billion (2004)</p> <p><i>Viral hepatitis</i> Mortality: 5,000 (Hepatitis B); 8,000-10,000 (Hepatitis C) Prevalence: 1.25 million (Hepatitis B); 3.2 million (Hepatitis C) with chronic infection (1999-2002)</p> <p><i>Alcoholic liver diseases</i> Mortality: 12,201 (2001) Years of potential life lost (YPLL): 316,321 (2001)</p>
Blood Diseases ¹²¹	<p><i>Sickle cell disease</i> Prevalence: 70,000; 1 in 500 African American births Thalassemia (includes Cooley's anemia)</p>

	<p>Prevalence: 1,000 Hemophilia Prevalence: 18,000 Incidence: 400 newborns each year</p>
<p>Musculoskeletal Diseases 122</p>	<p>Osteoarthritis Prevalence: 12.1% of adults (27 million) Osteoporosis Prevalence; 10 million adults, 80% of whom are women; 34 million have low bone mass Disability: > 1.5 million fractures Costs (direct): \$14 billion Osteogenesis Imperfecta Prevalence: 20,000-50,000 Paget's disease of bone Prevalence: 1 million</p>
<p>Skin Diseases and Conditions 123</p>	<p>Prevalence: At any given time, 1 in 3 people has a skin condition. Total health care costs: > \$29.1 billion (2004) Atopic dermatitis Prevalence: 10-20% of children and 1-3% of adults are affected Total health care costs: > \$3 billion</p>
<p>Eye Diseases 124</p>	<p>Age-related macular degeneration Prevalence: 1.75 million; leading cause of vision loss in persons age 65 or older (2004) Uveitis Prevalence: 115.3 cases per 100,000 persons (2004) Disability: 30,000 new cases of blindness (1990) Diabetic retinopathy Prevalence: 4.1 million adults aged 40 or older (2004) Glaucoma Prevalence: 2.2 million</p>
<p>Deafness 125</p>	<p>Hearing loss Prevalence: 2-3 of 1,000 newborns; 17% (36 million) adults; 15% (26 million) adults aged 20-69 suffer hearing damage due to noise exposure Otitis media (middle ear infection) Cost: \$5 billion Balance and dizziness Prevalence (balance): 4% (8 million) Prevalence (dizziness): 1.1% (2.4 million) Cost: \$8 billion for falls by older adults</p>

<p>Dental and Craniofacial Disorders¹²⁶</p>	<p>TMJ disorder Prevalence: 5-12% of the population; twice as prevalent in women as men Cost: \$4 billion</p> <p>Chronic periodontitis Prevalence: 80% of adults with 1 in 5 having severe periodontitis</p>
<p>Mental Disorders¹²⁷</p>	<p>Mental disorders Prevalence: 6% of adults (approximately 12.5 million) have a serious mental disorder Disability: No. 1 leading cause; accounts for 24% of all disability adjusted life years (DALYs) (U.S. and Canada, ages 15-44) Cost: \$198 billion annually in lost earnings; total direct and indirect annual costs of mental illness are more than \$300 billion</p> <p>Depression Prevalence: Major depressive disorder affects approximately 6.7% of American adults (approximately 14.8 million people) Disability: leading cause among mental health disorders; accounts for 7.5% of all DALYs (North and South America) Cost: \$36.2 billion due to lost work; \$51.5 billion including lost productivity while at work</p>
<p>Alcohol Use Disorders¹²⁸</p>	<p>Alcohol use disorders Prevalence: 19.3 million (7.8% of the population aged 12 or older)</p> <p>Alcohol-attributable chronic disease Total costs: \$155 billion (est.) Disability: Alcohol use is the 7th leading cause of DALYs</p>
<p>Addiction¹²⁹</p>	<p>Total cost: > \$600 billion (est.; includes health- and crime-related costs as well as losses in productivity)—approximately \$181 billion for illicit drugs, \$193 billion for tobacco, and \$235 billion for alcohol.</p> <p>Abuse or dependence on alcohol and illicit drugs Prevalence: 22.2 million people or 9% of the population aged 12 or older (SAMHSA/NSDUH 2008)</p> <p>Cigarette smoking Mortality: 443,000 (CDC Fast Facts Sheet)</p>
<p>Pain¹³⁰</p>	<p>76.2 million, or 1 in every 4 Americans, have suffered from pain that lasts longer than 24 hours in the past month and millions more suffer from acute pain. One in 10 persons with pain reports it lasting for a year or more.</p>

¹²² All statistics refer to the U.S. population unless otherwise specified.

¹²³ For more information, see <http://www.nhlbi.nih.gov/about/factbook/toc.htm> (chapter 4. Disease Statistics);

<http://www.nhlbi.nih.gov/health/dci/index.html>.

¹¹⁴ For more information, see <http://www.nhlbi.nih.gov/about/factbook/toc.htm> (Chapter 4, Disease Statistics); <http://www.nhlbi.nih.gov/health/dci/index.html>; Weiss KB. *J Allergy Clin Immunol* 2001;107:3-8, PMID: 11149982. http://www.cdc.gov/nchs/data/series/sr_10_235.pdf; <http://www.cdc.gov/mmwr/PDF/ss/ss5608.pdf>; <http://www.nhlbi.nih.gov/resources/docs/07-chtbk.pdf>.

¹¹⁵ For more information, see http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.

¹¹⁶ For more information, see <http://win.niddk.nih.gov/statistics/index.htm>; National Center for Health Statistics, Chartbook on Trends in the Health of Americans. Health, United States, 2006. Hyattsville, MD: Public Health Service; 2006.

¹¹⁷ For more information, see <http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm>; Levey AS, et al. *Ann Intern Med* 2009;150:604-12. PMID: 19414839. PMCID: PMC2763564; United States Renal Data System 2008 Annual Data Report. www.usrds.org/adr.htm.

¹¹⁸ For more information, see <http://kidney.niddk.nih.gov/statistics/uda/index.htm>; <http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm>.

¹¹⁹ For more information, see <http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/BurdenofDisease/DigestiveDiseases>; <http://digestive.niddk.nih.gov/statistics/statistics.htm>.

¹²⁰ For more information, see http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55_19.pdf; http://www.cdc.gov/ncidod/diseases/hepatitis/resource/dz_burden.htm; <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm>; Minino AM, et al. *National Vital Statistics Report* 2007;55:1-119. PMID: 17867520; Sandler RS, et al. *Gastroenterology* 2002;122:1500-11, PMID: 11984534.

¹²¹ For more information, see <http://www.nhlbi.nih.gov/health/dci/index.html>; <http://www.cdc.gov/ncbddd/hbd/thalassemia.htm>

¹²² For more information, see Lawrence RC, et al. *Arthritis Rheum* 2008;58(1):26-35. PMID: 18163497; http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/default.asp; http://www.niams.nih.gov/Health_Info/Bone/default.asp; <http://nihseniorhealth.gov/osteoporosis/toc.html>. For more information, see Bickers DR, et al. *J Am Acad Dermatol* 2006;55(3):490-500. PMID: 16908356; Larsen FS, Hanifin JM. *Immunol Allergy Clin North Am* 2002;22(1):1-2; Mancini AJ, et al. *Pediatr Dermatol* 2008;25(1):1-6. PMID: 18304144.

¹²⁴ Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):564-72. PMID: 15078675; Gritz DC, Wong IG. *Ophthalmol* 2004;111(3):491-500. PMID: 15019324; Nussenblatt RB. *Int Ophthalmol* 1990;14(5-6):303-8. PMID: 2249907; Kempen JH, et al. *Ophthalmol* 2004;122(4):552-63. PMID: 15078674; Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):532-8. PMID: 15078671.

¹²⁵ For more information, see <http://www.nidcd.nih.gov/health/hearing/>; <http://www.nidcd.nih.gov/health/statistics/quick.htm>; <http://www.nidcd.nih.gov/health/balance/>.

¹²⁶ For more information, see <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain>; <http://www.nidcr.nih.gov/OralHealth/Topics/GumDiseases/PeriodontalGumDisease.htm>.

¹²⁷ For more information, see http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part4.pdf; Kessler RC, et al. *Arch Gen Psych* 2005;62(6):617-27. PMID: 15939839; Greenberg PE, et al. *J Clin Psychiatry* 2003;64(12):1465-75. PMID: 14728109; Kessler RC, et al. *Am J Psychiatry* 2008;165(6):703-11. PMID: 18463104. PMCID: PMC2410028; Insel TR. *Am J Psychiatry* 2008;165(6):663-5. PMID: 18519528.

¹²⁸ For more information, see <http://pubs.niaaa.nih.gov/publications/economic-2000/alcoholcost.PDF>; <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm>; Grant BF, et al. *Arch Gen Psychiatry* 2004;61(8):807-16. PMID: 15289279; Michaud CM, et al. *Popul Health Metr* 2006;4:11. PMID: 17049081; Rehm J, et al. *Lancet* 2009;373(9682):2223-33. PMID: 19560604.

¹²⁹ For more information, see Office of National Drug Policy. The Economic Costs of Drug Abuse in the United States: 1992-2002. Washington, DC: Executive Office of the President (Publication No. 207303); CDC Fast Facts at http://www.cdc.gov/tobacco/data_statistics/fact_sheets/ast_facts/index.htm; SAMHSA/NSDUH at <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.cfm>; Rehm J, et al. *Lancet* 2009;373(9682):2223-33. PMID: 19560604.

¹³⁰ National Health Interview Survey, 2006, public use data file. Available at <http://www.cdc.gov/nchs/nhis.htm>; <http://www.cdc.gov/nchs/pressroom/06facts/06facts.htm>.