CANCER

CHANGING THE CONVERSATION

The Nation’s Investment in Cancer Research

AN ANNUAL PLAN AND BUDGET PROPOSAL FOR FISCAL YEAR 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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## CONTENTS

1. **Foreword: Changing the Conversation**
2. **Cancer Biology**
3. **Prevention and Screening**
4. **Care and Treatment**
5. **The NCI Portfolio**
6. **Partnering for Progress**
7. **Preparing a New Generation for Cancer Research**
8. **Provocative Questions**
9. **Profiles of Six Cancers: Introduction**
   - **Melanoma**
   - **Glioblastoma**
   - **Acute Myeloid Leukemia**
   - **Neuroblastoma**
   - **Lung Cancer**
   - **Ovarian Cancer**
10. **Revitalizing the Nation’s Cancer Clinical Trials System**
11. **Director’s Afterword**
12. **Budget**
Advances accrued over the past decade of cancer research have fundamentally changed the conversations that Americans can have about cancer. Although many still think of a single disease affecting different parts of the body, research tells us—through new tools and technologies, massive computing power, and new insights from other fields—that cancer is, in fact, a collection of many diseases whose ultimate number, causes, and treatment represent a challenging biomedical puzzle. Yet cancer’s complexity also provides a range of opportunities to confront its many incarnations.

We now know that cancer is a disease caused by changes in a cell’s genetic makeup and its programmed behavior. Sometimes these changes are spontaneous, and sometimes they arise from environmental or behavioral triggers, such as ultraviolet radiation from sunlight or chemicals in tobacco smoke. We have at hand the methods to identify essentially all of the genomic changes in a cell and to use that knowledge to rework the landscape of cancer research, from basic science to prevention, diagnosis, and treatment.

This knowledge brings us—and our national conversation—to a crucial opportunity for acceleration in the study of cancer and its treatment. The emerging scientific landscape offers the promise of significant advances for current and future cancer patients, just as it offers scientists at the National Cancer Institute—and in the thousands of laboratories across the United States that receive NCI support—the opportunity to dramatically increase the pace of lifesaving discoveries where progress has long been steady but mostly incremental. Some of the important scientific discoveries and their potential implications are recounted in the pages that follow.

The scientific puzzles we work to solve are illustrated in this document through profiles of six cancers in which the arc from basic research to clinical utility to patient outcomes is especially evident. We could have picked other cancers, and in future reports we undoubtedly will, but each of these profiles highlights the unique contribution that federal investment through NCI has made and can make.
In this report we also hope to spark a broader conversation about the value of the nation’s portfolio of investments in efforts to control cancer—from basic research, to prevention and diagnosis, to education about cancer causes and cancer care and treatment, to the support of cancer survivors. Indeed, we have a lot to talk about.

While those perspectives are only beginning to inform the American public’s perception about cancer and its treatment, the trajectory of cancer deaths reflects real and sustained reductions over the past decade or so for numerous cancers, including the four most common: breast, colorectal, lung, and prostate. We have identified proteins and pathways that different cancers may have in common and represent targets for new drugs for these and many other cancers—since so often research in one cancer creates potential benefits across others. And we have made great strides in strategies to prevent cancer (such as quitting smoking and limiting hormone replacement therapy), and to detect cancer earlier, when treatment is more effective and outcomes more favorable.

We reap the rewards of investments in cancer made over the past 40 years or more, even as we stake out a bold investment strategy to realize the potential we see so clearly. No matter what the fiscal climate, NCI will strive to commit the resources necessary to bring about a new era of cancer research, diagnosis, prevention, and treatment.

A fair share of those resources will be committed to the technical work required to understand the full dimensions of the molecular basis of cancer, coupled with the intricate analyses that translate that understanding into actionable strategies to reduce the burden of cancer. And we are continually reminded that cancer research, perhaps more than the study of any malady, involves the deepest knowledge of human biology.
Cancer Biology

Cancer is a disease of cells gone awry, of uncontrolled proliferation, of the loss of normal patterns of cell behavior. Cancer arises from a series of genetic and epigenetic changes (usually DNA-associated proteins that influence gene expression) that endow the cancer cell with its malignant behavior. During their transformation from normal to cancer, tumor cells undergo a large number of key changes. At the simplest level, cancer cells divide at inappropriate times. They don’t respond to the stop and go signals that normal cells do. In their development into tumors, they acquire a range of characteristics that help them survive, proliferate, invade, and grow. These changes include the production of new blood vessels (angiogenesis) to bring needed nutrients for continued tumor growth, and also include physiological actions that block the body’s attempts to get rid of cancerous cells through immunological responses. The tumor develops into what researchers now realize is essentially a new tissue—perhaps even analogous to a new organ—becoming a complex mixture of tumor and normal cells in the tumor microenvironment that help support the existence and continued proliferation of the embedded cancer cells. And, most devastatingly, cancer cells learn to move from their initial home to new, sometimes distant, sites in the body.

Despite these complexities and challenges, scientists now have a rapidly growing knowledge of the biology of a vast array of cancers, across a wide range of sites, both in solid tissue and blood. Some cancers exhibit characteristic changes, while changes in other cancers may be more heterogeneous. What are the changes? What causes each change? Where in its unnatural life cycle is a cancer cell most vulnerable? It is a hugely complicated set of questions. But it is also a list against which we have made huge strides.
The study of cancer biology must be as diverse as the stages of tumor development and the panoply of diseases being studied. Understanding the biology of cancer requires intensive work at the laboratory bench, in the cold room, at the computer, and at the blackboard. It utilizes such diverse tools as cells grown in culture, frozen human tissues, and organisms as simple as fruit flies or yeast. It involves dialogues and conversations, in person and in the scientific literature. NCI’s cancer biology research—initiated largely by investigators in hundreds of NCI-funded laboratories across the U.S.—helps build the basic knowledge of normal and cancerous cells, developing an ever-deeper understanding of biological mechanisms that may provide the basis for clinical applications to follow. We support and coordinate research projects at NCI and at universities, hospitals, research foundations, and businesses across the U.S. and abroad. This lofty mission starts with the simplest of questions: What is—and isn’t—normal? From such deceptively simple questions, the study of cancer biology builds the foundation for progress in cancer prevention, screening, diagnosis and treatment.

Cancer research today, especially on the frontiers America’s cancer researchers are renowned for spearheading, requires investment at a scale unimaginable 40 years ago.

The study of cancer biology touches on a number of important threads. Researchers study cancer-related mechanisms of DNA damage and repair, and investigate tumor immunology, as well as other responses of the body to cancer, and the biology of malignancies of the immune system. They identify interactions of cancer cells with the host microenvironment, and seek to better understand the molecular mechanisms of tumor growth and progression to more aggressive behaviors, such as angiogenesis, invasion, and metastasis. They develop genetically engineered mouse models of cancer to understand the progression of cancers and test interventions in intact organisms, and they analyze cancers as complex systems via computational models.

The discoveries of basic biology in cancer are usually more than a simple step away from clinical application. These are the scientific advances, however, that drive further research into new drugs and treatments—the backbone, if you will, of progress for patients in the future.

To help illustrate the power of this dynamic research engine, we present two stories to show the dynamic nature of this field and the way that cancer research gets done.
How do tumor cells acquire their new characteristics? One way is through the acquisition of mutations in their genes that, in turn, lead to production of abnormal proteins. In this way, cancer cells can co-opt, or highjack, a normal physiological process and generate new characteristics that help them survive or proliferate. Cancer biologists continue to identify and characterize these types of mutations.

Even more importantly, if the mutant IDH proteins are eliminated from cells, the cells revert to their normal behavior. To gain more insight into how IDH gene mutations affect the growth and survival of cancer cells, and building on other NCI-funded basic research, the Broad Institute of MIT and Harvard is participating in NCI’s Cancer Target Discovery and Development Network (http://ocg.cancer.gov/programs/ctdd.asp), to identify small molecules that block the production of hydroxyglutarate by mutant IDH proteins.

IDH, an enzyme (a protein that speeds up, or catalyzes, chemical reactions in the body) plays an essential role in converting simple carbohydrates into the molecule that the cell uses as a key energy source. About two years ago, mutations in the \textit{IDH} gene were identified in glioma, a type of brain cancer. Prior to that time, scientists were not aware that IDH and the pathway in which it works played an essential role in the development of any cancer. Since then, however, more than 70 percent of low-grade gliomas and secondary glioblastomas (more aggressive tumors that arise from low-grade gliomas) have been found to have mutations in the \textit{IDH} gene. Research has also confirmed that some cases of two other very different tumor types, acute myeloid leukemia, a cancer of the blood and bone marrow, and lung cancer, carry mutations in these genes.

The enzyme activities of the proteins produced by mutant forms of the \textit{IDH} gene are different from those of normal proteins. IDH normally changes the simple carbohydrate isocitrate into a new compound, ketoglutarate. The mutations make this enzyme dysfunctional. Instead of making ketoglutarate, IDH now consumes ketoglutarate and makes a third compound, hydroxyglutarate. One consequence of this difference is that the tumor cells with \textit{IDH} gene mutations produce much more hydroxyglutarate and much less ketoglutarate, metabolic changes common to cancer cells. These two compounds regulate a wide range of biological processes, such as how the cells use sugars or iron and how they respond to oxygen levels. In essence, these changes force cells to take on the energy metabolism of cancer cells.
Another area of intense research in cancer cell biology is aimed at understanding how tumors evade the body’s immune system, its natural defense against infections and other diseases, including cancer.

The immune system is comprised of white blood cells, including B-cells and T-cells, natural killer cells, macrophages, and dendritic cells, as well as other components; it can usually control or destroy invading bacteria and viruses. But cancer cells often evade that fate, because they resemble normal, healthy cells in enough ways to impede immune responses from being directed against them. In addition, even as tumors grow and their cells develop more and more genetic mutations, in effect becoming more “foreign” to the body, they can suppress the function of normal cells in their microenvironment to further thwart the immune system’s ability to attack and destroy cancer cells. Over the past decade, NCI funding has supported a number of researchers studying ways to strengthen the body’s immune response against tumors or harness the power of the immune system.

This therapeutic strategy, called immunotherapy, often involves the use of laboratory-made antibodies, so-called monoclonal antibodies, that hone in on specific proteins or antigens located on the surface of cancer cells. When the antibodies bind to their corresponding antigens on cancer cells, they can alert the immune system that the cancer cells are foreign invaders that must be eradicated. Binding of these antibodies to cancer cells may also disrupt communications systems inside the cells, causing the cells to self-destruct. Although some antigens targeted in this manner are also found on the surface of normal cells, they are often much more abundant on cancer cells, making them excellent targets for immunotherapy.

One particularly well known monoclonal antibody, trastuzumab (Herceptin), developed in the 1990s, can exert its anti-cancer effects by several mechanisms, including targeting a cell-surface protein called HER2. This protein was first identified over a decade earlier when researchers studying cancer in rodents discovered that the rodent version of HER2 contributed to the development of tumors, which led to the subsequent recognition in humans that approximately one-quarter of women who develop breast cancer have tumors that produce much more HER2 than normal (referred to as HER2-positive). These cancers are particularly aggressive, but trastuzumab treatment greatly improves the overall survival of many women with HER2-positive disease and is usually administered in combination with, or after treatment with, conventional chemotherapy and possibly radiation.

As with much of the research NCI funds, findings about one kind of cancer can translate into advances against others. In 2010, the Food and Drug Administration approved the use of trastuzumab to treat HER2-positive stomach cancer after a clinical trial showed patients treated with this antibody had improved survival. Stomach cancer is a notoriously difficult to treat cancer, and trastuzumab is the first promising new therapy approved for this disease in two decades.

The monoclonal antibody trastuzumab was developed in part through NCI-supported research.
Cancer systems biology applies computational and mathematical modeling to better understand the complexities of cancer. Its growth has been spurred over the past few years by significant technological advances in high-throughput techniques, such as microarrays, next generation genome sequencing, and techniques used to analyze protein interactions with DNA.

Traditional engineering sciences use computational modeling to predict what effects a broken wire will have on an electronic circuit. In the same fashion, cancer systems biology modeling can predict what effects various anti-cancer drugs will have on a cell or a patient. Traditional approaches to drug design rely primarily on linear logic or one-gene models, but blocking one target molecule is not always sufficient, because cells often find alternative routes to escape the blockage. This is one reason why many current drug design strategies fail. The systems biology approach is well suited for analyzing diseases such as cancer, which involve a large number of genes and pathways interacting via complex networks. Many researchers believe that a systems biology approach has the potential to overcome the limitations of linear models and identify new options for cancer treatment.

Computational modeling works by investigating the relationships between the pathways that control the cell’s response to inflammation, growth factors, DNA damage, and other events. The goal is to create a dynamic model of the biological processes related to cancer initiation, progression, and metastasis. The resulting data are then applied to sophisticated mathematical, statistical, and computational methods, and the results are used to predict patients’ responses to new drugs. “With computational models, you might be able to intelligently guess what will and won’t work for a patient before you try it,” said Paul Spellman, Ph.D., a researcher at Lawrence Berkeley National Laboratory, supported in part by the NCI Integrative Cancer Biology Program, or ICBP. “It offers the chance to learn about biological phenomena that might take thousands of hours in the laboratory to discover.” These types of advances are critically dependent on NCI-funded research, such as the ICBP, which currently funds nine Centers for Cancer Systems Biology.
THE CANCER GENOME ATLAS

Near the end of 2005, NCI and the National Human Genome Research Institute announced plans for an intriguing new initiative. Each committed $50 million over several years to what would be a pilot project, designed to determine whether large-scale sequencing, followed by intricate analysis and characterization, could accelerate understanding of the molecular basis of cancer. It was an ambitious undertaking, conducted through a network of more than 150 researchers at dozens of institutions across the nation, including a biospecimen resource to collect, process, and distribute tissue samples; genome sequencing centers; and genome characterization centers, which are identifying larger-scale genomic changes, such as gene copy number changes (increases and decreases), gene expression, DNA modification, and chromosomal translocations that can lead to cancer’s development and progression. The first types selected for study were brain, ovarian, and lung cancers.

Fewer than three years after its announcement, The Cancer Genome Atlas (TCGA, as it was nicknamed) delivered its first results. In glioblastoma multiforme, the most common—and deadly—form of brain cancer, TCGA researchers identified three previously unrecognized mutations that occur in the disease with significant frequency, along with core pathways that are disrupted in glioblastoma. The results, based on the genomes of 206 patients, also pointed to a potential mechanism of resistance to a chemotherapy drug commonly used in glioblastoma. A follow-up finding from this study, announced in 2010, showed that glioblastoma is not a single disease, but appears to be four distinct molecular subtypes, each susceptible to different treatments. This knowledge has potential, over time, to lead to therapies better tailored to each subtype.

TCGA’s science is providing the catalyst for further research that holds promise to affect the treatment of many forms of cancer—beginning with the knowledge of its genes and how they go wrong.

TCGA’s plan for the next few years is as ambitious in today’s environment as it was at the beginning: sequence, characterize, and understand the genomic changes of 20 or more additional tumor types.

In addition to looking at genetic changes, TCGA will also be exploring epigenetic changes, which involve the addition or removal of chemical tags and DNA-associated proteins to the DNA itself. These epigenetic changes can lead to the development and spread of cancer and are vital to the understanding of the cancer process.
“During my training as a pediatric oncologist at Cambridge University in the early 1990s, I was struck by how limited our knowledge was about the biology of childhood cancers.” That stark assessment, particularly the inability to know why some patients with a given type of cancer respond to treatment, while others do not, led Javed Khan, M.D., to the study of molecular biology—and ultimately to join the Pediatric Oncology Branch in NCI’s Center for Cancer Research.

Importantly, sequencing genomes of patients and tumors is a starting point. Once an alteration in a gene has been discovered, said Khan, further research needs to be done in order to determine whether that changed gene affects behavior in a cell. “The easiest mutations to understand are those that affect the protein-coding regions of DNA, which comprise 2 percent of the genome. That’s important because proteins can be good drug targets.”

“You have to sequence many hundreds of genomes to look for what’s commonly changed in that 2 percent,” added Khan. “And if it’s commonly changed, then you would hypothesize that’s actually an important area; this may be a gene that’s important for driving that tumor.” This type of change is known as a driver mutation. “It is most likely,” said Khan, “that most of the changes that we see are not going to be driver mutations; the majority of the changes are not going to be functionally significant. Perhaps five or 10 genetic alterations will be the drivers that become targets for future therapies in pediatric cancer.”

“I came to NCI to do a combination of clinical practice and cutting-edge science—what is now called translational medicine,” said Khan. That led him to genomics and recently to a sweeping effort in children’s cancers. Launched in 2010, the NCI-sponsored Pediatric Cancer Genome Project is sequencing the genomes of tumors from hundreds of children with cancer to discover genetic changes causing or driving the disease. The goal, Khan said, is to “identify the Achilles’ heel of these cancers.”

Researchers involved in this project are at St. Jude Children’s Research Hospital and the Washington University School of Medicine in St. Louis. St. Jude has a repository of biological samples and clinical information from children who have been treated there since the 1970s. The collection represents a treasure trove of information about cancer, and it can now be scrutinized using the latest genomic technologies.

Winnowing down a list of potential therapeutic targets will be one of NCI’s key contributions in the years ahead, posited Khan. The pharmaceutical industry, he said, will not follow every discovery of a single mutated gene. NCI and academia will primarily be the players responsible for validating the importance of gene mutations and alterations in cancer biology and resolving which are the ones best suited for drug development. It is, said Khan, all about a “translatable type of research.”
Prevention and screening represent the twin pillars of our pre-emptive defenses against cancer. Cancer prevention includes efforts to forestall the process that leads to cancer, along with the detection and treatment of precancerous conditions at their earliest, most treatable stages, and the prevention of new, or second primary, cancers in survivors. Cancer screening identifies either precancers or early cancers that are still highly amenable to treatment while the number of malignant cells is very small.

Research on cancer prevention and screening focuses on three main areas: developing early detection and screening strategies that result in the identification and removal of precancerous lesions and early-stage cancers; developing medical interventions, such as drugs or vaccines, to prevent or disrupt the carcinogenic process; and risk assessment, including understanding and modifying lifestyle factors which increase cancer risk. To illustrate our progress in this area, we present three examples—colorectal cancer screening, cervical cancer vaccines, and ending tobacco use—of different approaches to cancer prevention and screening that can dramatically reduce cancer burden.
Screening for Colorectal Cancer

A prime example of the power of prevention research is the substantial progress we have made in reducing colorectal cancer incidence and death, with new insights illuminating the way toward even greater reductions in the near future.

Colorectal cancer, currently the second leading cause of cancer death in this country, is frequently preventable and highly treatable if detected early. From 1975 through 2007, mortality from this disease declined by 40 percent in the U.S., due to changes in risk factors, increased screening, and advances in treatment. The Cancer Intervention and Surveillance Modeling Network (CISNET), sponsored by NCI’s Division of Cancer Control and Population Sciences, estimates that more than 50 percent of this decline can be attributed to screening tests, including fecal occult blood tests (FOBT), flexible sigmoidoscopy, and colonoscopy. These screening tests help reduce colorectal cancer mortality by identifying early-stage cancers and adenomatous polyps, which can be precursors to colorectal cancer, for removal.

Besides improvements in risk factor modification and treatment, there are substantial opportunities for improvements in colorectal cancer screening, through better adherence to screening recommendations and increased accuracy of screening tests. According to a 2008 survey conducted by the Centers for Disease Control and Prevention, only 64 percent of respondents age 50 or older reported having an FOBT within the preceding year or a sigmoidoscopy or colonoscopy within the previous 10 years. Factors that likely contribute to this lack of full compliance include limited access to affordable health care, resistance to dietary limitations imposed prior to screening, and aversion to bowel cleansing techniques and invasive procedures associated with colonoscopy and sigmoidoscopy.
Because no cancer screening test is 100 percent accurate, scientists continue to develop new screening tests and improve existing tests. In one cutting-edge area of research, scientists supported by the NCI Alliance for Nanotechnology in Cancer are trying to improve the accuracy of colonoscopy using gold-coated nanoparticles to target cancerous or precancerous cells in the colon wall before a visible growth has formed. Light emitted from the colonoscope would be reflected by the nanoparticles, allowing the abnormal cells to stand out better from the surrounding normal cells. The use of nanoparticles to deliver toxic agents to cancerous cells in the colon is also being investigated.

Another line of research focuses on the use of drugs or other agents to prevent colorectal cancer, especially among individuals at increased risk of this disease. Clinical trials sponsored by NCI’s Division of Cancer Prevention, Division of Cancer Epidemiology and Genetics, and Division of Cancer Treatment and Diagnosis, have already shown that nonsteroidal anti-inflammatory drugs (NSAIDs)—aspirin, celecoxib, and sulindac (plus difluoromethylornithine)—can reduce the incidence of new adenomatous polyps in people who have had one or more polyps removed previously. Moreover, a recent analysis of data from four clinical trials showed that aspirin taken for several years at a dose of at least 75 milligrams per day reduced colorectal cancer incidence and mortality. Because NSAIDs have been associated with a number of adverse effects, finding even safer, more-effective preventive agents than those already identified is an important emphasis of further research.

A Vaccine to Prevent Cervical Cancer

As recently as the 1940s, cervical cancer was a major cause of death among women of childbearing age in the U.S. Widespread introduction of the Papanicolaou test (better known today as the Pap test) in the 1950s, which allows early detection of abnormal and cancerous cells in the uterine cervix, helped reduce cervical cancer incidence and mortality in this country by more than 70 percent. Cervical cancer now ranks 14th as a cause of cancer death among American women.

Nevertheless, in certain populations and geographic regions of the U.S., cervical cancer incidence and death rates are still high, due in large part to limited access to cervical cancer screening and follow-up care. Cervical cancer incidence and death rates also remain high in developing countries, where more than 80 percent of cervical cancer cases occur. Worldwide, cervical cancer is the third most common cancer among women and the second most frequent cause of cancer-related death, accounting for nearly 300,000 deaths annually. As in this country, limited access to cervical cancer screening and follow-up care are significant factors contributing to the burden of cervical cancer.
In recent decades, increased understanding of how cervical cancer develops has led to major advances in the early detection and prevention of this disease. We now know that persistent infections with certain types of the human papillomavirus (HPV) are the cause of the vast majority of cases of cervical cancer. Scientists in NCI’s Division of Cancer Epidemiology and Genetics made crucial discoveries that led to this awareness, and scientists in NCI’s Center for Cancer Research pioneered techniques that enabled the development of two FDA-approved vaccines to prevent cervical cancer. These vaccines target two types of HPV that cause approximately 70 percent of cervical cancer cases worldwide, and one of the vaccines additionally targets two types of HPV that cause about 90 percent of cases of genital warts.

Scientists at NCI have made crucial discoveries that led to the awareness of how cervical cancer develops and pioneered techniques that enabled the development of vaccines to prevent the disease.

HPV infection causes several types of cancer—anal, vulvar, vaginal, and oropharyngeal—in addition to cervical cancer. There is potential for vaccines to prevent these other HPV-associated cancers.

Despite this success, much more needs to be done. At least 13 other types of HPV are classified as oncogenic, or high-risk for cancer. The approved HPV vaccines offer modest cross-protection against some, but not all of these additional high-risk virus types.

Developing new vaccines that provide broader and more effective cross-protection—ideally, against all oncogenic types of HPV—is a priority. The availability of vaccine formulations that are less costly to produce and might not require refrigeration would also encourage the implementation of vaccination programs more widely, especially in less developed countries.
Recent initial results from the National Lung Screening Trial (NLST), a randomized national study involving more than 53,000 current and former heavy smokers ages 55 to 74, demonstrated that screening with low-dose helical computed tomography (CT), compared to standard chest X-ray, resulted in 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT. These results of the NLST, sponsored by NCI at a cost of over $250 million over a period of eight years, provide a method to prevent death from lung cancer by screening people at especially high risk. In particular, those who have been heavy smokers may benefit the most from a helical CT, which can find small, potentially lethal lesions at early, treatable stages of the disease.

“This is the first time that we have seen clear evidence of a significant reduction in lung cancer mortality with a screening test in a randomized controlled trial. The fact that low-dose helical CT provides a decided benefit is a result that will have implications for the screening and management of lung cancer for many years to come,” said Christine Berg, M.D., NLST project officer at NCI.

The NLST was an extremely complicated study to coordinate. To ensure and enhance the representativeness of the results, NLST was conducted at 33 centers throughout the country. The expertise of designing and managing very large-scale clinical trials with very clear, closely monitored communication was something that demonstrated, yet again, the importance of a federal role in coordinating and managing a trial with tens of thousands of subjects.

A large number of detailed analyses of NLST data due out in 2011 should provide scientists with a deeper understanding of this disease, its causes, and other potential ways to reduce its burden. The NLST clearly offers a tool for the screening of high-risk people, along with a prescient reminder that the best way to avoid being at high risk is to avoid smoking.

As with all cancer clinical trials, the NLST provided answers to a set of specific questions related to a specific population. Whether those answers can be used to provide general recommendations for the entire population will be the subject of future analysis and study. The vast amount of data generated by NLST, which are still being collated and studied, will greatly inform the development of clinical guidelines and policy recommendations. Those, however, are decisions that ultimately will be made by other organizations.

According to Richard Fagerstrom, Ph.D., co-chief statistician for the NLST, “There are many other things that we will learn from this study, other than just whether screening with helical CT decreases lung cancer mortality. We will also get considerable information about the cost-effectiveness of the technique. This will be important input for third-party payers for the procedure, such as Medicare, to see whether this will actually be economical. This could have a major positive impact on the health care system as far as costs go.”

Fagerstrom also noted that there is a sizable amount of information to be parsed with respect to different kinds of specimens, including sputum, blood, and even urine. And the database is open to investigators at other institutions, not just those affiliated with the trial.

Important as these findings are, they will not curtail NCI’s efforts to reduce or eliminate the use of tobacco. Smoking cessation is still the best way to prevent death from lung cancer.
Curbing the Use of Tobacco

The area of cancer prevention that has the potential to yield the largest public health benefit in the U.S. and worldwide is accelerating efforts aimed at prevention and hastening cessation of tobacco use. Tobacco use, in particular cigarette smoking, is the nation’s leading cause of preventable death, not only from cancer but also from heart disease and several other conditions. Besides causing most cases of lung cancer, tobacco has been linked to cancers of the throat, mouth, nasal cavity, esophagus, stomach, pancreas, kidney, bladder, and cervix, among others. Tobacco use accounts for approximately 30 percent of all U.S. cancer deaths.

The prevalence of cigarette smoking in the U.S. remains unacceptably high, and the decline in tobacco use observed since the early 1970s has stalled in recent years. Current estimates of smoking prevalence for U.S. adults indicate that one in five smokes cigarettes.

Overall smoking prevalence figures mask vast disparities in tobacco use and lung cancer mortality when education level, race, ethnicity, and other factors are taken into account. For example, among all population groups in the U.S., black men have the highest death rate from lung cancer. Smoking rates in the U.S. are inversely associated with education: the higher one’s level of education, the less likely he or she is to smoke. For example, 41 percent of adults with the end-product of a high school education smoke, whereas only 6 percent of adults with a graduate degree smoke. Among military personnel, 42 percent of men between the ages 18 and 25 are smokers, while 22 percent of white servicemen between the ages of 18 and 24 use smokeless tobacco. These figures emphasize the need for new strategies and interventions to reduce tobacco use among population groups that have been only marginally influenced by existing strategies and interventions.

To address significant gaps in research on understudied and underserved populations relating to tobacco-related health disparities, NCI, in partnership with the American Legacy Foundation, created a network of researchers, the Tobacco Research Network on Disparities or TReND [http://www.tobaccodisparities.org]. One of TReND’s first research projects sought to develop an index to measure how various racial, ethnic, and socioeconomic groups are exposed to, and perceive, tobacco-related messages.

NCI supports a large portfolio of smoking cessation research and the National Network of Tobacco Cessation Quitlines [1-800-QUIT-NOW] and Smokefree.gov [http://www.smokefree.gov]. In 2009, NCI launched Smokefree Women [http://women.smokefree.gov] to provide evidence-based cessation guidance tailored to the needs of female smokers and to develop an online support community, utilizing websites for women who want to quit. NCI researchers are also working to help NCI-designated Cancer Centers improve delivery of cessation services to patients who smoke. Continued smoking in patients with cancer can reduce the effectiveness of cancer treatments, slow healing times, and increase the risk of second primary cancers.
Cancer’s burden is not equally distributed. There are differences in the incidence, prevalence, and mortality of cancer among specific population groups in the United States. The Center to Reduce Cancer Health Disparities (CRCHD) is the component of NCI dedicated to confronting those inequities, particularly in understanding how biological, environmental, social, and cultural factors contribute to differences in cancer prevention, care, and treatment.

One of CRCHD’s flagship programs, the Community Networks Program (CNP), features innovative partnerships among academic institutions, community organizations, and community-serving healthcare providers. For example, a program called CNP-Redes en Acción [Networks in Action] increased enrollment of children in clinical trials by 48 percent, and CNP-Hawaii demonstrated an increase in mammography screening rates from 35 percent to 62 percent among Filipino women through the use of educational billboards on buses.

Another CRCHD program of note is the Patient Navigation Research Program. A patient navigator, who could be a registered nurse, a social worker, or even a patient who has been treated for cancer at that center, acts as a guide through the often daunting treatment of cancer. Navigators work with patients, survivors, families, and caregivers to help them access and chart a course through the healthcare system, overcoming barriers to quality care.
GLOBAL HEALTH AND A GLOBAL PERSPECTIVE

No nation exists in a vacuum, and cancer is clearly a disease that defies borders. American researchers benefit from a broader perspective by engaging in research outside U.S. territories, just as international researchers make significant contributions to NCI’s overall mission while acquiring knowledge, skills, and abilities to enhance the research environment in their home countries.

The global burden of cancer is large and growing larger. Each year, more than 11 million people are diagnosed with cancer worldwide. By the year 2020, this number is expected to increase to 16 million. Cancer causes more than eight million deaths each year, or approximately 13 percent of all deaths worldwide. Within developing countries, cancer is projected to increase rapidly over the next few decades. Unless current trends change, cancer in developing countries is expected to represent 70 percent of the global cancer burden by the year 2030, a statistic driven by demographic shifts toward more elderly populations and the movement toward more Western lifestyles, most notably increased per capita tobacco consumption and higher-fat, lower-fiber diets.

A global cancer research perspective offers myriad opportunities that a U.S.-only research focus would not afford. For example, international studies enable us to investigate rare cancers—such as certain inherited, familial types of kidney cancer, melanoma, and other cancers—by providing access to much larger populations of patients than can be found within the confines of our national borders. A global perspective also expands the diversity of environments occupied by humans, providing unique opportunities to explore relationships between genes and specific environmental exposures, including infectious agents that may be associated with cancer.

We are often reminded today that the world is interconnected, politically and economically. Nations have obligations to each other, and biomedical research is no exception. NCI can help other nations confront and study their unique cancer burdens. In that vein, NCI will soon be strengthening its commitment, with the establishment of a center for global health.

The new center will have much to do, from addressing cancer burdens of nations with populations numbering many hundreds of millions, to overcoming the seemingly simple barrier of delivering vaccines to places that lack even the infrastructure for refrigeration of such medications.

Consider, for example, that sub-Saharan African countries are least prepared to address a growing cancer burden, yet 20 percent of cancers in Africa may be preventable, because they are linked to infectious agents such as viruses, bacteria, and parasites. Two overwhelmingly preventable cancers, liver and cervical, account for approximately 60 percent of the cancer-related deaths in eastern and western regions of Africa. In many areas of Africa, liver cancer is the top cancer for males and cervical cancer is the leading cancer for females. This kind of prevention will not be a simple matter, however. The lead time for the development of vaccines against cancer-causing agents is measured in decades. In the case of hepatocellular cancer caused by hepatitis B virus, to take just one example, there is a vaccine available; for hepatocellular cancer caused by hepatitis C, none yet exists.

There are other parts of the world where cancer risks are high, some even higher than in Africa; as an example, nasopharyngeal carcinoma is common in parts of Asia. By evaluating high-risk areas around the world, we have gained a better understanding of previously unknown risk factors and the underlying causes of cancer. Several such international studies are examining possible environmental and genetic risk factors in different populations, including exposures from polycyclic aromatic hydrocarbons, environmental pollutants that may contribute to increased incidence rates of a variety of cancers.

Looking at variations in cancer risk in children globally can also have striking implications. NCI-supported scientists, including Cheryl Willman, M.D., pathology professor at the University of New Mexico, have studied leukemia in Hispanic children. Some of these children have a significantly increased risk of relapse for acute lymphoblastic leukemia (ALL), which is independent of other prognostic factors. Findings from studies in this high-risk population characterized unique clusters of genes associated with the children who also have a high percentage of Native American ancestry. These studies also reveal the striking clinical and genetic heterogeneity in high-risk ALL and point to novel genes which may serve as new targets for diagnosis, risk classification, and therapy.
The development of more efficient and effective cancer treatments—treatments that destroy cancer cells while leaving surrounding healthy tissue unharmed—is a critical element of NCI’s research agenda, particularly the development of therapies tailored to the cancers of individual patients. While the immediate goal is cancer treatment, targeted interventions may ultimately have an important role in cancer prevention, as well.

Our understanding of the molecular changes in cancer is leading to the dawn of an age of genetically informed cancer medicine. We are now designing precise therapies to hone in on specific targets that drive tumor cell proliferation and survival, including not only targets in cancer cells, but also targets in surrounding cells, the so-called tumor microenvironment.

We are also learning that the complexity of molecular interactions within and among cancer cells, and between cancer cells and normal cells, will require refinement of multi-agent treatment approaches against cancer. As a result, development of future treatments will require innovative strategies and partnerships—among academics, the public sector, and industry. Fashioning this new approach will require NCI’s involvement and leadership at every step, particularly when it comes to combinations of experimental drugs produced by more than one company.
We are still in the early days of genetically informed cancer medicine. Much of the focus has been on the development of molecularly targeted therapies, such as imatinib (Gleevec) and trastuzumab (Herceptin). But cancer researchers and pharmaceutical and biotechnology companies are beginning to devote greater attention to another part of the therapeutic equation: the tests—or molecular diagnostics, as they are often called—that are needed to determine not only whether a patient’s tumor expresses the molecule being targeted, or whether it is mutated, but also whether the cancer cell’s overall mutational gene expression profiles predict a good response to the treatment.

It’s all part of the move away from nonselective therapeutics, explained Paul Mischel, M.D., a researcher at UCLA’s Jonsson Comprehensive Cancer Center. “If we’re dealing with therapies that target specific enzymes, the alterations in those enzymes and the pathways that they regulate are often different in patients with the same types of cancers, so having molecular diagnostics is essential to selecting optimal therapies,” he said.

In 2002, for example, an international research team that included scientists from NCI and the Sanger Institute in Britain, as well as other international partners, identified a specific mutation in a gene called BRAF that is present in about 60 percent of tumor samples from patients with metastatic melanoma, a disease with a poor prognosis and for which treatment advances have been rare. Additional laboratory studies showed that the mutated BRAF gene alone could transform normal cells into cancerous cells. These findings led researchers to develop several drugs that target the mutated BRAF gene. One of these drugs, PLX4032, has already moved into a phase III clinical trial, enrolling only patients whose tumor cells have mutations in the BRAF gene, based on the results of a diagnostic test. Earlier trials of PLX4032 had demonstrated promising results, with the majority of patients experiencing tumor shrinkage, including some patients in whom tumors were eradicated.

A drug called crizotinib has followed a similar path to PLX4032. Initially developed to treat tumors with mutations in a gene called MET, crizotinib also inhibits a protein called ALK that has been associated with the development of some cancers, including lung cancer. In 2007, in lab and mouse model studies, researchers showed that a genetic alteration in ALK—a fusion with another gene, EML4—could lead to inappropriate expression of ALK and to tumor development. They also found the EML4-ALK gene fusion in a small percentage of tumor samples from patients with one type of lung cancer. Based on the discovery, an early clinical trial testing crizotinib that was already enrolling patients was altered to enroll more patients with advanced lung cancer whose tumors had the ALK gene alteration. Based on the excellent response of these patients to crizotinib in this early trial, the drug is now being tested in a phase III clinical trial of patients with ALK-positive lung cancer.

The technological and logistical aspects of molecular diagnostics are not the only difficulty. There are numerous interconnected pathways in a cancer cell,” said Sheila Taube, Ph.D., of NCI’s Program for the Assessment of Clinical Cancer Tests. “If you cut off one pathway, there may be another pathway the cell uses to accomplish the same end,” said Taube. “So if you measure only one piece of a pathway that may be involved, that may not be sufficient to know whether the patient will respond to the drug.”
NCI and its partners are taking steps to enhance the process of drug development—from target identification and validation, to high-throughput screening and chemical design optimization, to testing in animal models, to the design of mechanisms for monitoring in vivo activity. At the end of the process is translation of discoveries into human clinical trials and treatments. The challenge now is to prioritize which targets to pursue and then to move them into an efficient platform for development. NCI’s mission is not to compete with the private sector. Rather, we work to develop therapies for both common and rare cancers that are not being vigorously pursued by industry. NCI’s resources, from chemistry to toxicology, are also of great utility for many academic researchers.

For the majority of cancer patients, surgery—often followed by radiation or chemotherapy—remains a key component of treatment and one that NCI is continually working to improve. One outcome of a major surgical study supported by NCI and its sponsored cooperative groups gained attention recently when it was shown that, for 20 percent of breast cancer diagnoses, extensive removal of cancerous lymph nodes from the axilla had no advantage. The surgery did not change treatment outcome, improve survival, or make the cancer less likely to recur, while it did increase recovery time and result in complications such as lymphedema and infection. Extensive lymph node removal proved unnecessary because the women in the study had chemotherapy and radiation, which probably eliminated any disease in the nodes.

Many chemotherapy drugs used in breast and other cancers over the decades have their foundations in NCI research. Today, NCI’s Chemical Biology Consortium, a network of institutions that have formally agreed to collaborate, is working in the early phases of the drug discovery process in high-throughput screening studies to identify small molecules that have anticancer activity. This integrated research consortium stands at the interface of chemical biology and molecular oncology.

As potential treatments—drug-like small molecules, large biologic molecules, and those that target immunologic function—emerge, researchers will need to develop new ways to assess their efficacy and establish the proper treatment regimens. Likewise, NCI is aggressively seeking to enhance the clinical trials system to better accommodate targeted therapies and accurately assess genomic changes in patients.

We can expect that over time, tailored treatment that depends on the molecular profile of the tumor will become the norm for most malignancies. The challenge is finding the best match between the tumor and therapeutic regimen for each patient. The field is taking steps now to ensure that in the years ahead, targeted therapies are available for many types of cancer.
The diagnosis and treatment of cancer, already complex in nature, are made all the more difficult by the fact that many patients also have other diseases. According to recent research, much of which was funded by NCI grants, these co-morbidities—particularly diabetes, hypertension, and obesity—are common in breast, prostate, colorectal, and lung cancer patients, especially in those who are older and of lower socioeconomic levels. Studies also show an increased risk of death in patients with co-morbidities, as these patients often have poorer prognoses and fewer treatment options.

Patients with multiple diseases are typically disqualified from clinical trials, thereby restricting researchers who study co-morbidities to the use of observational data.

Early on, NCI recognized an opportunity to work within this limitation. NCI researchers have refined already-existing indices of co-morbidity and enhanced older analyses, resulting in an easy-to-implement measurement algorithm for co-morbidity. This new tool permits investigators using databases such as NCI’s SEER-Medicare data registry to study the four most common cancers tied to co-morbidity in a more in-depth and efficient manner.

Consider another example of a co-morbid cancer condition about which we’re gaining greater knowledge. Chronic obstructive pulmonary disease (COPD) is a well-established risk factor for lung cancer, and both diseases are strongly linked to smoking. Recent genome-wide association studies (which search across the genome for common, small variations in inherited genes) have identified a genetic region on chromosome number 15 that is associated with smoking behavior, lung cancer, and probably COPD. NCI-supported research is underway to better understand whether this region helps to regulate smoking behavior, which can modify the risk for both lung cancer and COPD.

Genome-wide association studies are also uncovering genetic loci that are linked to diseases not previously thought to be related to one another: Variants of genes CDKN2A and CDKN2B are now associated with contributing to the risk of melanoma and type 2 diabetes. A variant of another gene, CDKAL1, is linked to type 2 diabetes and prostate cancer, and the gene JAZF1 to type 2 diabetes and prostate cancer. While these studies are still mostly in their early stages, linking different diseases to the same common genes or gene variants could point toward common treatments in the future.

Much research remains to be conducted before scientists can develop treatments to help patients struggling with co-morbidities and individuals with multiple chronic conditions.

“There is a compelling need to better understand the prevalence and consequences of cancer co-morbidities, especially given the rising rates of other chronic conditions such as obesity and diabetes,” said Robert Croyle, Ph.D., director of NCI’s Division of Cancer Control and Population Sciences. “Clinicians need evidence-based guidance concerning complex patients who don’t match the characteristics of patients enrolled on clinical trials. Multidisciplinary coordinated care shows promise for patient management, but we’ll have to expand trials and observational data collection to answer the many questions we have about co-morbidities.”
AN IMAGING AGENT REBORN

Since 2009, the halt in operations of several nuclear reactors caused a global shortage of isotopes commonly used in medical imaging and diagnostic procedures, particularly in cancer. In the rush for a solution to the shortage, NCI played a new and vital role.

Many diagnostic imaging tests, including bone scans that utilize Single Photon Emission Computed Tomography (SPECT), require the use of tracers. Bone scans are essential tools in the diagnosis of bone metastases in cancer patients, especially those with cancers (such as breast and prostate) that tend to metastasize to bone.

In January 2011, FDA approved a New Drug Application (NDA) from NCI for a previously approved drug, Sodium Fluoride F18, to be used in bone scans. The NDA is the vehicle through which drug sponsors formally propose that the FDA approve a pharmaceutical for sale and marketing in the U.S. and was required at this time, because this would be a new use for this substance. In contrast to the only previously approved radioactive tracer for bone scans, Sodium Fluoride F18 is not subject to the supply problems that led to the recent nationwide shortages of the more commonly used tracer, Tc-99m.

Sodium Fluoride F18 is more expensive than the other tracer, but it can be produced in medical cyclotrons, which are available at many research universities and commercial suppliers in the United States. This drug also provides better images because it uses Position Emission Tomography (PET) instead of SPECT imaging, allowing for improved, earlier detection of abnormalities.

In bringing this imaging agent to FDA for approval, NCI made an agent available that, because of its high development costs coupled with its limited market, no commercial entity had an interest in developing. NCI moved forward with this drug approval for public health reasons and to facilitate treatment of rare diseases. New Drug Applications are expensive for a variety of reasons, including the cost of clinical trials to demonstrate safety and efficacy of the new substance, filing fees, and manufacturing and distribution costs, all of which could easily amount to many millions of dollars.
Fast Facts for Advances in Cancer Treatment

New drugs and clinical trials
- 12 new drugs or drug uses were approved for oncology by the FDA in 2010.
- 348 phase III oncology trials are ongoing in the U.S.
- 861 cancer medicines from industry are in some step of the trial process (2009 data).
- 2,000-plus clinical trials accepting children and young adults are in progress.
- 200-plus prevention trials are open.
- 100-plus screening trials are open.

Selected 2010 highlights and trends in drug development.
- The first-ever therapeutic cancer vaccine was approved.
- Drug inhibitors for specific targets, such as BRAF and ALK genes, are being developed.
- There are a vast number of new targeted therapies entering trials.
- Advances in understanding drug resistance are being turned into new therapies.
Extramural Research: Funding and conducting innovative research are the highest priorities at NCI. The NCI Extramural Research Program reaches nearly 650 universities, hospitals, Cancer Centers, and other sites throughout the U.S. and more than 20 other countries. Over 80 percent of NCI’s current budget funds extramural research activities. NCI has six divisions and several key centers.

Five of the divisions oversee and coordinate extramural activities:

- The Division of Cancer Biology provides funding for research that investigates the basic biology behind all aspects, including the causes, of cancer.

- The Division of Cancer Control and Population Sciences supports a comprehensive program of genetic, epidemiologic, behavioral, social, and surveillance cancer research.

- The Division of Cancer Prevention supports research to determine and reduce a person’s risk of developing cancer, as well as research to develop and evaluate cancer screening procedures.

- The Division of Cancer Treatment and Diagnosis works to identify and translate promising research areas into improved diagnostic and therapeutic interventions for cancer patients.

- The Division of Extramural Activities coordinates the scientific review of extramural research funding applications and provides systematic surveillance of that research after awards are made.

Intramural Research: A portion of NCI’s research dollars supports the work of scientists in the two intramural sections:

- The Center for Cancer Research is home to more than 250 scientists and clinicians, organized into more than 50 branches and laboratories, conducting basic, clinical, and translational science to advance knowledge of cancer and AIDS. The Center’s researchers translate their discoveries into clinical applications by utilizing the infrastructure provided by the NIH Clinical Center, the largest clinical research hospital in the world.

- The Division of Cancer Epidemiology and Genetics conducts population and multidisciplinary research to discover the genetic and environmental determinants of cancer and new approaches to cancer prevention.

In addition to the six divisions and the Center for Cancer Research, NCI’s Office of the Director contains a number of offices that perform important functions and provide services across the institute, including bioinformatics, training, health disparities, and HIV/AIDS, among others, and supports research in several high-technology areas through the Center for Strategic Scientific Initiatives.
### Funding Categories for Fiscal Year 2010

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<th>Funding Category</th>
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<th>% of Total</th>
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<td>Research Project Grants</td>
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<td>Intramural Research</td>
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<td>Total FY2010 Budget</td>
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Figures for FY2010 exclude American Recovery & Reinvestment Act (ARRA) funding.
In February 2009, after President Obama signed into law the American Recovery and Reinvestment Act, NCI began to face the kind of problem most of us would love to have: spending an unexpectedly large amount of money. The recovery act—or ARRA, as it became known—provided NCI with approximately $1.3 billion in additional funding over its annual appropriation, to be allocated over a two-year period. This special allocation was a welcome infusion, but one that also altered funding expectations for the years to follow.

ARRA spending carried with it some particular concerns, not the least of which was separately managing two-year economic stimulus funds alongside NCI’s annually appropriated budget. ARRA was, first and foremost, about jobs and hiring, about sustaining and building the American workforce. NCI committed approximately $747 million, or 60 percent of ARRA funds, to the support of 573 research grants, through supplements to existing, longer-term grants and to new, competing research proposals, many funded for two years. Mindful of our responsibility to increase the scientific workforce, NCI also invested in new faculty awards to NCI-designated Cancer Centers and to minority institution/NCI Cancer Center partnerships.

In scientific terms, however, two years is a very short time. This is, after all, a field that generally makes incremental progress, building experiment on experiment, publication on publication, with most projects carried out over a multiyear period. In planning for ARRA spending, NCI’s leaders were well aware that many two-year grantees would apply for extensions or follow-on research in years ahead. Likewise, there was a clear expectation that many unsuccessful, but meritorious, ARRA applications would be revised and resubmitted for conventional research support. In short, we continually asked ourselves: How much appropriated money will we have in the years ahead to support work begun under ARRA?

That’s still a somewhat open question, as we wait to see what appropriations and application pools look like in the near future. In a continued time of economic difficulty, however, careful scrutiny will be key, even in the most optimistic of scenarios.

NCI’s planning for ARRA was not built solely around grants; the institute funded a number of new initiatives and, importantly, added to some ongoing grants so that a certain amount of risk in the years beyond those for which funding was designated was lessened.

In particular, The Cancer Genome Atlas, already a prominent program, received ARRA funding from NCI and its sister institute, the National Human Genome Research Institute, to begin to identify all of the relevant genomic alterations in 20 or more tumor types. Reflecting its significance, the National Institutes of Health named TCGA as one of its seven signature ARRA projects and Vice President Biden named it as the No. 2 ARRA project for the nation. Other NCI ARRA investments included the funding of nearly 40 early-phase clinical trials of new, molecularly targeted treatments; enhancement of the NCI Community Cancer Centers Program; development of methods of banking biological samples and for creating bioinformatics platforms; efforts to bring scientists from other disciplines to the study of cancer; and supplemental funding for NCI-designated Cancer Centers.
Promising laboratory discoveries, the foundation of biomedical science, begin a lengthy process to translate scientific knowledge into new treatments for cancer patients. Along that path, from the laboratory to the clinic, NCI supports a number of important initiatives across the United States.

NCI’s Cancer Centers, which currently number 66 facilities nationwide, are largely based in research universities that are home to many of the hundreds of NCI-supported scientists who conduct a wide range of intense, laboratory research into cancer’s origins and development. Their work is echoed throughout this document.

The Cancer Centers Program focuses on trans-disciplinary research, including population science and clinical research. Those centers with a comprehensive designation, of which there are currently 40, must have a robust portfolio of research in basic, population, and clinical research, and must additionally demonstrate professional public education activities in the communities they serve.

Many of the Centers are also treatment facilities that deliver the latest medical advances to patients, including the support of cancer survivors and outreach out to underserved populations. Cancer Centers, like all NCI programs, are subject to peer review each time they apply for renewal of their support grants.

The NCI Community Cancer Centers Program came into existence to test the concept of a national network of community cancer centers to expand and deliver advanced care in local communities.

NCI’s Clinical Community Oncology Program (CCOP) connects more than 3,000 community-based physicians at nearly 400 hospitals in 34 states and Puerto Rico with academic investigators, to accelerate implementation of NCI-sponsored cancer treatment, prevention, and control clinical trials. By providing community level access to clinical trials CCOPs boost the participation of underserved populations.

NCI’s Minority-based Community Oncology Program, a companion program to the CCOP, is focused in areas where physicians serve sizable minority populations.
Progress in cancer research depends upon partnerships—in the use of new technologies; in collaborations to advance experimental techniques; in innovative methods of helping fund the earliest stages of development of small companies working in the cancer field; and in the testing of new molecular agents in cancer patients. Supporting partnerships touches NCI programs too numerous to mention encyclopedically, but certainly includes programs such as those detailed on the next few pages.

NCI’s Experimental Therapeutics Program (NExT) makes available to outside researchers—from academia and industry—research resources not readily available at most medical centers. These resources can shave years from the 10-year to 12-year development cycle of a new drug, as well as help bring down the nearly billion-dollar development cost of many cancer drugs. NExT is also facilitating the earliest phase of clinical testing in humans, known as phase 0, which tests new, molecular agents in sub-therapeutic doses, in small numbers of patients, to see whether potential new anticancer agents hit their intended targets.

As a model of working with industry to promote and develop new drugs, the first substance tested as part of a phase 0 trial was the drug ABT-888, a drug candidate that inhibits a cancer protein called PARP, which was provided by Abbott Laboratories. “The successful and expeditious conduct of this trial, and the impact it has had on the development timeline of ABT-888 at Abbott, provide an initial example of improved therapeutics development in oncology,” said James H. Doroshow, M.D., director of NCI’s Division of Cancer Treatment and Diagnosis, who spearheads the NExT program. NCI is also utilizing the phase 0 trial to test new imaging agents.
Molecular Technologies

As an example of another partnership, in 1998, NCI established the groundwork for a program focused on technology development to meet the needs of cancer researchers and clinicians.

Taking risks on early-stage, potentially transformative technologies, the Innovative Molecular Analysis Technologies (IMAT) program has contributed to many technologies that are now on the market and in frequent application across cancer research and clinical communities. As with other NCI programs, IMAT subjects all applications to competitive peer review.

Commercial products now in widespread use, such as RNALater, Affymetrix gene chips, Illumina bead platforms, and Quantum dot labeling to monitor complex interactions within living cells, were considered high-risk ideas when initially funded through the IMAT program. Yet, their current availability and applicability to multiple clinical and basic sciences research settings are a testament to the pay-off that such transformative technologies have provided to the field of cancer research.

To take just one example of the program’s success, James Landers, Ph.D., professor of chemistry at the University of Virginia, used IMAT funding to help develop a technology for T-cell lymphoma diagnosis he calls a “lab on a chip.” This highly integrated system is capable of detecting infectious agents present in complex biofluids in less than 30 minutes, and the diagnosis of certain blood cancers in under an hour.
Small Business Innovation

Funding is a vital component of any partnership, and NCI has become one of the largest sources of early-stage cancer research technology financing in the U.S. Its Small Business Innovation Research (SBIR) program, along with the closely allied Small Business Technology Transfer Program, are NCI’s engines for developing and commercializing novel technologies to prevent, diagnose, and treat cancer.

The two programs seek to increase small business participation and private sector commercialization of technology developed through federal research and development. The SBIR program has made great strides in confronting one key funding gap between the end of an award and the subsequent round of private financing needed to advance a product or service toward commercialization. To cover this gap, NCI’s unique Bridge Award is specifically designed to incentivize partnerships between second phase SBIR awardees and third-party investors and strategic partners. The Bridge Award more than triples the amount of funding available to SBIR applicants, and has often proved an entrée into private funding.

One of the first companies to receive NCI Bridge funding was Florida-based Altor BioScience Corp., which is advancing the discovery and development of targeted immunotherapeutic agents for the treatment of cancers, viral infections, and inflammatory diseases. Altor used funding from a $3 million SBIR Bridge grant to support clinical development of ALT-801, an immunotherapeutic agent.

In January 2011, Altor announced it had raised more than $10 million in private financing to complete multiple phase II clinical trials of the new agent. In looking for such investments, companies “have their own due diligence,” said Altor chief executive Hing C. Wong, Ph.D., “but they always love to see what NIH thinks about the product and the technology. They really like that kind of validation.”
To the casual observer, biomedical imaging still means devices such as a CT scan or X-ray: technology that looks inside the body to visualize everything from broken bones to masses inside organs. For Anna Wu, Ph.D., of the Crump Institute for Molecular Imaging at UCLA, today’s most advanced molecular imaging technologies are “tools to look at very specific biological questions in living people.”

Wu is the founder of, and chief scientific advisor to, a small California-based biotechnology and nanotechnology company called ImaginAb, Inc., which is focused on developing a new class of highly targeted proteins for imaging and therapy, based on engineered antibody fragments.

Antibodies, which detect and help destroy invaders, are substances that can also be engineered to bind to the molecules on the surface of cells that display specific proteins. The antibodies may be used therapeutically to prevent tumor growth by blocking specific cell receptors or by delivering chemical doses to a specific target. What ImaginAb has done is to reformat antibodies into smaller fragments suitable for diagnostic imaging in order to target a given cancer. These small antibody fragments are tied to a positron emitting isotope that allows for molecular imaging of cancer cells using PET (Positron Emission Tomography).

NCI’s SBIR program, through its competitive peer review process, made ImaginAb one of its SBIR funding awardees. That infusion, says Wu, “has been invaluable to the company’s survival and growth. The NCI funding helped us move forward at a very tough time when investment capital was simply not available.” Today, ImaginAb has major global companies as clients and has re-engineered over a dozen therapeutic antibodies into fragments for imaging and possibly for novel therapies.
Preparing a New Generation for Cancer Research

Together, NCI’s training programs span basic research, investigational therapeutics, and population-based studies. The NIH is, in many ways, analogous to a large research university. Its investigators are often referred to as faculty, and many of its scientists are able to qualify for tenure in the intramural programs of their institutes.

The largest program is run by the Center for Cancer Research, which, as part of the NCI intramural research program, offers fellowships for training in the basic and translational sciences, as well as in the clinic on the NIH campus. About 1,300 fellows are enrolled in the program each year. For clinical fellows, the NIH Clinical Center brings together, under one roof, the treatment of patients with laboratory science—a unique arrangement for researchers who typically don’t get to do both clinical and basic research on the same research project.

In addition to providing intramural training, the NCI Center for Cancer Training (CCT) is dedicated to building cancer research capacity at institutions across the nation and fostering the next generation of the cancer research workforce—a diverse, multidisciplinary workforce. NCI supports a range of fellowships, Career Development Awards, Institutional Training Awards, and Institutional Education Awards to help early-stage scientists and clinicians become independent investigators and to encourage senior scientists to become mentors for their younger colleagues.

NCI also has a long history of bringing students into the labs on the NIH campus in Bethesda, Md. Each summer, the campus is infused with new faces of undergraduates and graduate students who spread out in labs and clinics. Several years ago, these opportunities were expanded to include gifted high school students.

Training also takes place beyond the NIH campus in Bethesda. NCI’s campus in Frederick, Md., runs student internship programs that enroll local high school students over the summer and during the school year.
This has been a challenging and hopeful time for NCI to lead the nation’s cancer research program. Over the past two decades researchers have unraveled some of the mysteries that happen to the genome of a cancer cell and how a cancer cell behaves in its local environment. With better understanding and recent technological advances in many fields, such as genomics, molecular biology, biochemistry, and computational sciences, progress has been made on many fronts, and a portrait has been made of many cancers. With sustained and accelerated funding, NCI can build upon today’s cancer advances with provocative thinking by asking research questions that build on recent discoveries.

NCI is reaching out to researchers in various disciplines to pose and articulate “provocative questions” that can help guide the nation’s investment in cancer. Provocative questions may be built on older, neglected observations that have never been adequately explored, or on recent findings that are perplexing, or on problems that were traditionally thought to be intractable but now might be vulnerable to attack with new methods.

Through face-to-face meetings and a public website, the Provocative Questions initiative is intended to engage NCI’s scientific community in serious debate and energize NCI’s many constituencies. Here are some of the questions that have been discussed at workshops and online:

- What molecular mechanism(s) are responsible for the well-documented association of obesity with certain types of cancer?
- Why are some disseminated cancers cured by chemotherapy alone?
- Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?

You can read, submit, and comment on questions at: http://provocativequestions.nci.nih.gov.
The progress achieved against the six cancers that are profiled in this section exemplify NCI’s investment in scientific research, from basic and population science to applications in prevention and cancer care. The stories of these cancers illustrate how molecular and genomic data have enhanced identification of cancer subtypes and provided insight into potential therapeutic targets, yielding tangible benefits for patients, sometimes in less than 10 years from the time of genetic discovery to initial clinical trials. Every cancer has a different part of the story to tell—whether it is simply the ability to distinguish which patients would benefit from more aggressive therapy, as with acute myeloid leukemia, or a new drug with potential therapeutic benefits for two different cancers, as with neuroblastoma and lung cancer. The element tying these stories together is the role of NCI.

While we made great progress in some of the cancers highlighted in this section, there are others that continue to be more formidable. It is for these cancers that NCI’s continued support cannot be underestimated. We are just beginning to untangle the mysteries underlying these diseases, and we must maintain that momentum to make progress that could lead to new screening, diagnosis, or treatment techniques. Such progress is achievable, but not inevitable. Each passing year brings real progress, but also deeper understanding of how difficult these diseases are to conquer. Continued progress will require heightened dedication to using science to better understand and counteract the collection of diseases we call cancer.

**MELANOMA**

The majority of skin cancers are basal or squamous cell carcinomas, which together are also designated as non-melanoma skin cancers. Most forms of non-melanoma skin cancer are highly curable and can be prevented by reducing sun exposure. Sun exposure can also increase the risk of melanoma, a form of skin cancer that begins in melanocytes, the cells that produce melanin. Although melanoma accounted for fewer than 70,000 of more than two million cases of skin cancer in 2010, it caused more deaths than any other type, with an estimated 8,700 deaths in 2010. Over the past 30 years, the incidence of melanoma in the U.S. has nearly tripled.

The majority of melanoma patients are diagnosed with localized disease, and surgery is curative in most localized cases. The significance of early detection of melanoma, when it is still at a localized stage and treatable, cannot be minimized. However, melanoma patients with advanced metastatic disease rarely survive more than a year after diagnosis, with a five-year survival rate of 15 percent.

Outcomes for advanced-stage melanoma have not improved substantially for decades, but results of recent clinical trials suggest that new therapeutic strategies may change this trend. In August 2010, Plexxikon, a small drug development company, announced that one of its drugs—PLX4032—had elicited a response in more than 80 percent of melanoma patients in an early-phase clinical trial. PLX4032 caused the tumors in 24 of the 30 trial participants to shrink by at least 30 percent, while the tumors of two patients disappeared.
Just a few months later, evidence of the drug’s effectiveness grew even stronger: a clinical trial involving hundreds of participants across many institutions showed that metastatic melanoma patients treated with PLX4032 lived longer than those who had been given the chemotherapy drug dacarbazine, which is the current standard of care.

Taking a closer look at the research that made this promising drug possible provides a powerful example of how basic cancer research is translated into therapeutic potential. PLX4032 is a molecularly targeted therapy, a drug that is intended to be used to change the activity of a specific molecule or group of molecules. This drug was designed to inhibit the activity of a mutant form of a protein called BRAF. BRAF is the most commonly mutated gene in melanoma (mutated in over half of all melanomas) and is also mutated to a lesser degree in at least a few other cancer types, including lung cancer.

Knowledge of the BRAF protein as a pro-growth signaling molecule emerged initially from years of basic laboratory research. Subsequently, BRAF gene mutations in melanoma were discovered by scientists in the United Kingdom in 2002, and these mutations were shown to render the BRAF gene oncogenic. The high prevalence of BRAF gene mutations in melanoma made it a candidate therapeutic target and, according to Harvard Medical School professor and NCI-funded investigator Lynda Chin, M.D., was a transformative event that helped spur enthusiasm for cancer genome sequencing. This newfound enthusiasm eventually grew into large-scale efforts such as The Cancer Genome Atlas.

Early attempts to target BRAF in melanoma were unsuccessful in the clinic, in part because the drugs used interfered with BRAF function in both cancer and normal cells. To address this issue, a team that included NCI-supported investigators used high-throughput screening, in combination with structural biology, to identify compounds that inhibit the activity of the mutant form of the BRAF gene found in most melanomas, but have little effect on the BRAF gene found in normal cells. This research demonstrated that it is possible to selectively target the mutant form of the BRAF gene with PLX4032. The results from the phase I clinical trials testing the efficacy of PLX4032 were published just eight years after the discovery of the BRAF gene mutation.

Clinical researchers will continue to evaluate PLX4032 in patients, and additional laboratory research will be conducted in parallel to gain insight
Research continues to contribute to the body of knowledge on the mechanisms that drive malignant cell behavior. Understanding these mechanisms may lead to targets other than the \textit{BRAF} gene. For example, germline mutations in the \textit{p16} gene have been identified in about half the patients with familial melanoma. A recent genome-wide association study identified three additional genes associated with risk of melanoma. As illustrated with the example of PLX4032, NCI plays a pivotal role in rapidly moving drugs through the full arc of research from the laboratory to the clinic. NCI support is critical to continued efforts to build on the successes of drugs such as PLX4032 so that clinical results can fuel the cycle for the next generation of promising new drugs for melanoma.

**MELANOMA RISK ASSESSMENT TOOL**

An online Melanoma Risk Assessment Tool is now available to help physicians assess a person's risk of developing the disease. Developed by a group of researchers from NCI, the University of Pennsylvania School of Medicine, Memorial Sloan-Kettering Cancer Center, and the University of California, San Francisco, the tool uses easily obtainable information to estimate a person's risk of developing skin cancer within the next five years. The research team identified several factors that can predict skin cancer risk, including geographic area, hair color, complexion, sunburn type, tan type, age, and moles and freckling.

The program (available on the NCI website at http://www.cancer.gov/melanomarisktool), uses a complex mathematical formula to calculate risk, and allows doctors to quickly and easily identify patients at increased risk for developing melanoma (and indirectly for other skin cancers), who could then undergo interventions, such as a complete skin exam, special counseling to avoid sun exposure, regular self and professional surveillance of moles, or participation in clinical trials for skin cancer prevention.
IMMUNOTHERAPIES FOR MELANOMA

In a simple sentence, the New York Times on March 25 reported a significant step against a feared cancer: “The first drug shown to prolong the lives of people with the skin cancer melanoma won approval from the Food and Drug Administration on Friday.”

The new drug, Yervoy (ipilimumab), was developed by James Allison, Ph.D., who is today head of the immunology program at the Memorial Sloan-Kettering Cancer Center in New York. The new medication stands out in its mechanism of action, as well. “The treatment,” Allison told the New York Times, “is of the immune system, it’s not of the tumor.”

For more than two decades, Allison has studied the mechanisms that regulate the immunologic responses of T lymphocytes, which are commonly referred to as T-cells; he works to manipulate T-cell response, in order to develop novel tumor immunotherapy approaches.

“The success of ipilimumab underscores the importance of basic research to clinical achievement,” Allison said in a statement. “The concept came directly out of our studies on fundamental mechanisms of regulation of T-cell responses.”

According to the FDA, “Yervoy’s safety and effectiveness were established in an international study of 676 patients with melanoma.” Patients were randomly assigned to receive one of three treatment regimens: Yervoy plus an experimental tumor vaccine called gp100, Yervoy alone, or the vaccine alone. Those who received the combination of Yervoy plus the vaccine or Yervoy alone lived an average of about 10 months, while those who received only the experimental vaccine lived an average of 6.5 months.

Prior to the recent approval, treatments for melanoma were more limited, given that many melanomas are relatively resistant to standard chemotherapeutic agents. Two FDA-approved drugs, interleukin-2 (IL-2) and dacarbazine, produced a response in only 10 percent to 20 percent of patients.

Other approaches to stimulate immunity against tumors use a technology called adoptive T-cell therapy. During this therapy, specific T-cells from the immune system of the patient, or a matching donor, are harvested from the blood. The T-cells are then activated outside the body in the laboratory to recognize tumor cells and destroy them. The modified T-cells are then infused back into the patient and are “adopted” by the body to enhance its natural immune system. This treatment approach is being tested in various early-stage and late-stage clinical trials. NCI trials, led by Steven Rosenberg, M.D., Ph.D., chief of surgery at NCI, tested adoptive transfer therapy in melanoma by transfusing patients with tumor-specific T-cells called tumor infiltrating lymphocytes.

Rosenberg believes adoptive T-cell therapy may prove a useful tool in cancers beyond melanoma. “We have demonstrated that gene-modified T-cells can recognize and kill melanoma cells over-expressing a specific antigen, leading to a clinical response in some patients,” said Rosenberg. “With these trials, we hope to extend this type of immunotherapy to patients with more common cancers, such as breast and colon.”
Cancers of the brain are relatively rare but often devastating diseases; just 1.5 percent of malignant primary cancers originate in the brain. Glioblastoma multiforme (GBM) is the most common form of primary brain cancer and is one of several types of glioma, a tumor type that arises in cells of the brain and spine called glial cells. In the U.S., roughly 11,000 people are diagnosed with primary GBM every year. Though GBM rarely metastasizes to other organs, it spreads aggressively within the brain and is more deadly than most other brain malignancies.

Patients with newly diagnosed GBM generally respond poorly to conventional treatments and have a median survival of approximately one year following diagnosis. Recently, research has proceeded from small, incremental improvements to greater progress in our understanding and treatment of GBM. Through the coordinated efforts of NCI-funded initiatives—including The Cancer Genome Atlas, the Glioma Molecular Diagnostic Initiative (GMDI) and the Repository of Molecular Brain Neoplasia Data (REMBRANDT)—scientists have collected and molecularly characterized an unprecedented number of these rare tumors. Analysis of TCGA sequencing data revealed that GBM is not a single disease but has at least four molecular subtypes: proneural, neural, classical, and mesenchymal. Because different cellular pathways are affected in these subtypes, differences in treatment responses are observed. This finding is paving the way for more informed selection of therapies for GBM patients, who have traditionally all been treated the same way because their tumors look alike under a microscope.

TCGA has also identified connections between features such as the age of the patient and molecular subtype. The proneural subtype is associated with younger patients, mutations in the IDH1 and TP53 genes, and resistance to chemotherapy and radiation.

Alternatively, the classical subtype with abnormalities in the EGFR gene has shown the best response to therapy. The next step is to...
determine how to leverage advanced diagnostic procedures, such as molecular profiling, and to identify various GBM subtypes and match them with more appropriate patient therapies. Drugs that affect some of these pathways are available and, though promising in theory, have had mixed results in clinical trials.

The difficulty of translating information about genetic abnormalities into successful treatments underscores the need for a viable laboratory model of GBM. It has been difficult to culture these cells in a manner that retains their unique characteristics and molecular profiles. Recently, researchers from the NCI intramural program and other institutions isolated rare cells from glioma tissues that resemble normal neural stem cells but have all the genetic abnormalities of the tumor. These “cancer stem cells” likely will be a better model for studying GBM and screening hundreds of drugs or combinations of drugs than the traditional cancer cell lines used until now. The hope is that improved cancer models will speed the availability of treatments to patients.

Angiogenesis, the formation of new blood vessels, is a critical process during the development of nearly all tumors, including GBM. As a tumor continues to grow, it needs a sufficient supply of nutrients that can only be provided by the development of new blood vessels to the tumor. By understanding the mechanisms of angiogenesis, potential therapeutic targets can be identified. Bevacizumab (Avastin) became the first FDA-approved agent that was specifically developed as an angiogenesis inhibitor. NCI played a key role in promoting the use of bevacizumab for the treatment of GBM—the first new FDA-approved treatment for recurrent GBM in nearly 30 years.

In the future, tumors like GBM will no longer be defined solely under the microscope, but also on the basis of their molecular characteristics. As we expand molecular diagnostics to the full GBM genome, NCI will continue to play a pivotal role in providing resources and expanding the scientific infrastructure to apply findings to inform the next steps of discovery.
Over the past 20 years, scientists have developed and refined a great wealth of laboratory techniques, such as PCR (a process that amplifies DNA or RNA) and protein and DNA microarrays comprised of small chips dotted with thousands of microscopic pieces of DNA, thus spurring the next generation of technological tools—molecular profiling. Molecular profiling uses an amalgamation of these techniques and others, to provide a more comprehensive picture of an individual tumor's characteristics. Some of these characteristics include mutations or other changes in the DNA sequence, epigenetic changes, and unique patterns in the expression of thousands of genes and proteins. By providing a molecular map of an individual cancer, molecular profiling may allow clinicians to determine the origin of a cancer, its potential for metastasis, its drug responsiveness, and the probability of its recurrence, resulting in treatment strategies tailored specifically to individual patients.

NCI-supported researchers were among the first to demonstrate that molecular profiling could help classify similar types of cancers. They used two different types of leukemia—acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)—as test cases to demonstrate the utility of this approach. Distinguishing AML from ALL is critical for successful treatment, and although the distinction between AML and ALL has been well established, there is no single test that is sufficient to establish the diagnosis and identify the tumor type. Current clinical practice involves interpretation of the tumor's morphology and other physical characteristics, which are determined by several specialized tests. Although usually accurate, errors occur, and leukemia classification remains imperfect. By using a more systematic approach to classify cancer—molecular profiling—researchers were able to not only distinguish between the two types of leukemia, but also to predict their responsiveness to chemotherapy. Molecular profiling has the potential to offer significant improvements in the molecular diagnosis and targeted treatment of the disease, providing a useful supplement to existing diagnostics.

Numerous other NCI studies have used molecular profiling techniques to further classify two types of diffuse large B-cell lymphoma (DLBCL)—the most common type of non-Hodgkin lymphoma. These cancer types are indistinguishable when first diagnosed, but are clinically very different as the disease progresses: 40 percent of patients respond well and exhibit prolonged survival while 60 percent do not. Led by Louis Staudt, M.D., Ph.D., head of NCI's Molecular Biology of Lymphoid Malignancies Section, a team of researchers from several institutions used molecular profiling to show that there is significant diversity among the tumors of DLBCL patients. They identified two molecularly distinct forms of DLBCL and associated each form with a clinical outcome. These profiles were then used to develop mathematical predictors, which accurately divided patients into two categories—those with good and those with poor prognoses—and proved to be a more powerful tool than the standard methods for the identification of high-risk patients.

The potential of molecular profiling is not limited to leukemia and lymphoma; progress is being made with molecular profiling of many solid tumors as well. However, much research still needs to be done before this tool can be used routinely in the clinic.
More than 12,000 Americans were diagnosed with AML in 2010, and nearly 9,000 died from the disease. Following diagnosis, patients with AML have an overall five-year survival rate of 23 percent.

AML is a cancer of the bone marrow that develops when a type of precursor cell, the myeloblast, proliferates unchecked and fails to differentiate, resulting in accumulation of myeloblasts in the bone marrow and blood. AML is characterized by a high degree of genetic alterations—about half of patients with AML have chromosomal changes or rearrangements that can be seen by special staining procedures and visualized under the microscope (karyotyping). AML illustrates the key role of NCI support in untangling the myriad mutations that underlie cancer. Discovering these mutations is the first step in the development of new treatments.

Recent advances in understanding the genetics of AML have moved diagnosis beyond karyotyping to molecular profiling (see molecular profiling box), resulting in improved classification and stratification of cancer subtypes. Molecular profiling refers to a series of high-throughput techniques that scientists use to measure many characteristics of the cell, essentially giving a snapshot of the cell at the moment of the test, which includes extensive characterization of DNA through sequence analysis, determination of whether there are extra copies of some genes, and assessment of other changes to DNA or DNA-associated proteins that may influence gene expression (sometimes called epigenetic changes). In addition, it is possible to gain insight into pathways that are active in a cell by measuring levels of proteins and messenger RNA (the templates from which proteins are formed), as well as looking at patterns of expression of microRNAs, which are small RNA molecules capable of regulating gene expression. Piecing together the information provided by molecular profiling will provide the map that eventually may guide us to new therapies for AML.

In 2003, Timothy Ley, M.D., professor of genetics at Washington University in St. Louis, and his colleagues applied for an NCI grant to sequence all of the genes in the normal and leukemic cells of patients with AML. At the time, sequencing...
the entire genome of cancer patients was an extremely expensive and ambitious concept. Despite debate as to what might be learned, NCI supported the proposed research. Ultimately, Ley’s team identified a mutation in the gene for DNA methyltransferase 3A (the DNMT3A gene) in the tumor cells of AML patients who did not exhibit any large-scale chromosomal changes. DNA methyltransferases add molecules called methyl groups to DNA, which can influence DNA structure and activity. High levels of methylation in regions of DNA that control expression of specific genes often result in lower levels of expression of those genes.

This particular DNMT3A gene mutation is associated with poor outcomes for AML and can be used to make treatment decisions: for patients with a DNMT3A gene mutation, chemotherapy is not the best treatment option. These data suggest that molecularly informed therapies will be selected for a patient’s individual cancer, resulting in a therapy that would likely have the highest efficacy.

Subsequently, in 2009, Ley’s team linked mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2 genes), which had previously been found in glioblastoma, to AML. Within a year of the IDH1/2 gene mutation discovery in AML, studies conducted by a group partly funded by an NCI specialized cooperative center grant designed to bring together physical scientists, engineers, cancer biologists, and oncologists in collaboration with a pharmaceutical company, revealed that these mutations resulted in the excess production of the cellular metabolite, 2-hydroxyglutarate (2HG). Studies suggest that IDH1/2 gene mutations may not be the first step in development of either AML or glioblastoma but are potential drivers for tumor progression. As this profile illustrates, understanding the molecular changes underlying cancer can provide the foundation for ultimately improving the way we deliver therapy and identifying new targets for therapy.

“It’s an amazing time in cancer research. I’m convinced that some of the findings are so clear and so informative and have such a tremendous potential to change things that I think it’s possible only to be optimistic about the future.”

— Tim Ley, M.D., Professor of Genetics, Washington University in St. Louis
Looking back on discoveries made in just the last decade or two, it’s easy to see the hope—and promise—that the future holds. For example, we know much more about both genetic alterations (changes to the DNA sequence, changes in gene copy number, and rearrangements of chromosomal DNA) and epigenetic changes (persistent changes in gene activity that result from the addition or removal of chemical tags and DNA-associated proteins to DNA that affect how and when genes are turned on or off) and how these changes lead to initiating development and spread of cancer.

The initiation and progression of cancer are controlled by both genetic and epigenetic changes; however, unlike genetic alterations, epigenetic changes are potentially reversible. Following the approval of several drugs that target specific molecules involved in the epigenetic regulation of gene expression, the use of epigenetic targets is emerging as a valuable approach to chemotherapy as well as chemoprevention of cancer.

Normal epigenetic modifications encompass two major types of changes: DNA methylation and modifications to the components that make chromosomes, or chromatin, each of which is altered in many cancer cells. As a result, cells cannot appropriately control gene expression (genes are repressed when they should be activated or activated when they should be silent) and thus cell proliferation can occur at inappropriate times, augmenting cancer development.

The potential reversibility of epigenetic modifications suggests that they are viable targets for the treatment of cancer, and a small number of drugs that target epigenetic changes have been developed over the years. An NCI developmental research grant supported the development of vorinostat (Zolinza), which targets histone modifications and it, along with a second inhibitor for histone modifications, romidepsin (Istodax), has been FDA approved for the treatment of T-cell lymphoma. A recent study suggested that vorinostat also possesses some activity against recurrent glioblastoma multiforme, resulting in an improved median overall survival of 5.7 months. Decitabine (Dacogen) and azacitidine (Vidaza), which target DNA methylation, have been approved for the treatment of myelodysplastic syndrome—a pre-cancerous state that frequently leads to deadly cancer of the bone marrow. A few years ago, the latter diagnosis was a death sentence. Today, patients have a good chance of remission with fewer side effects than offered by conventional chemotherapy. These drugs offer the potential for chemoprevention, by reversing epigenetic changes before they lead to full-blown cancer.
Each year about 700 children in the U.S. are diagnosed with neuroblastoma (which comprises about 7 percent of pediatric cancers), and approximately 200 children die of the disease. Little is known about risk factors for neuroblastoma, though 1 percent to 2 percent of patients have a family history of neuroblastoma. The rarity of the disease makes NCI’s involvement in funding research and developing new therapies particularly critical, as pharmaceutical companies are unlikely to invest in diseases for which there is a small potential market.

As we have been learning for many cancers, neuroblastoma is not a single disease. Researchers have identified three biologically distinct types of neuroblastoma. The three risk categories for neuroblastoma—low, intermediate, and high—which indicate patient prognosis, are based in part on these biological types. High-risk neuroblastoma accounts for about half of all cases and is the most challenging to treat. Most cases of high-risk neuroblastoma occur in children one year of age and older. Five-year survival rates in children one year of age or older have improved, increasing from 35 percent in the period from 1975 to 1978 to 65 percent from 1999 to 2002. Despite improvements in survival, current therapy is not adequate for about half of children with high-risk disease.

Developing new therapies for high-risk neuroblastoma has posed a significant challenge; until recently, these children had few treatment options other than escalating doses of chemotherapy and radiation therapy. Other cancers are informing potential therapies for neuroblastoma, as some mutations are shared across disease types.

Just this past year, results from an NCI-funded Children’s Oncology Group (COG) clinical trial demonstrated that ch14.18, an antibody that binds to a cell surface protein called GD2, is effective for children with high-risk neuroblastoma when given in conjunction with other immune-boosting drugs. An approximately 10 percent increase in two-year survival (which went from 75 percent to 86 percent) was observed among patients who had been treated with the antibody and immune-boosting drugs compared with those who had been treated with standard therapy. The initial discovery that most neuroblastoma cells express GD2 on their surfaces was made in the 1980s, but translation of this finding into a successful therapy took nearly two decades. Because GD2 is not found in more common cancer types, pharmaceutical companies exhibited little interest in making the ch14.18 antibody. Instead, NCI manufactured and provided the antibody for the phase III trial that demonstrated efficacy and continues to manufacture the

A neuroblastoma cell viewed with a scanning electron micrograph; the cell has a rough surface with many finger-like cytoplasmic projections.
"NCI’s role in the success of this trial went far beyond funding. The COG team that led the clinical trial had access to a unique and outstanding resource: NCI’s drug production facility, where NCI scientists manufactured the antibody because no private-sector company was willing to do so."

— John Maris, M.D., Director, Center for Childhood Cancer Research, Abramson Family Cancer Research Institute

antibody for ongoing COG trials.

The translation of ch14.18 from discovery to the clinic took 20 to 25 years; however, under the right circumstances, development of new therapies can occur more rapidly. In 2008, an NCI-funded laboratory discovered that mutations in the anaplastic lymphoma kinase (ALK) gene cause the majority of hereditary neuroblastoma cases. In addition, the ALK gene is mutated or amplified in approximately 7 percent of sporadic neuroblastoma cases. While many genetic discoveries are heralded as promising targets for screening or therapy, the ALK’s gene potential as a therapeutic target was quickly exploited. The ALK gene is also mutated, through a different mechanism (fusion with another gene by chromosomal rearrangement), in about 3 percent to 5 percent of non-small cell (NSCLC) lung cancers (see lung cancer profile). The potential of the ALK gene as a target for NSCLC in addition to neuroblastoma resulted in increased interest in developing drugs against the ALK gene and quickly led to the launch of a COG phase I clinical trial of crizotinib, an ALK inhibitor that had demonstrated success in a lung cancer phase I trial—just one and a half years after the initial genetic discovery in neuroblastoma.

Much attention has been focused on genetic discoveries such as the ALK gene findings, but understanding basic biology can also lead to new interventions. Researchers in NCI’s intramural program observed that retinoids (derivatives of vitamin A) imposed growth control and induced differentiation in neuroblastoma cells grown in the laboratory. By investigating the mechanisms leading to differentiation, scientists discovered that retinoic acid was inducing chemoresistance through a cellular survival signaling pathway involving the AKT family of protein kinases. Inhibition of AKT with a small molecule called perifosine slowed cell growth and sensitized tumors to chemotherapy.

Identification of leads for testing in future clinical trials likely will stem from continued efforts to understand the basic biology that drives tumor formation. One aspect of neuroblastoma that intrigues researchers is the fact that many low-risk tumors resolve spontaneously, suggesting that the body is capable of eliminating at least some cells that go awry. Uncovering the mystery of spontaneous regression might have implications for the prevention and treatment of neuroblastoma and other cancers in the future.
An estimated 220,000 individuals were diagnosed with some form of lung cancer in 2010. It is the leading cause of cancer-related death, with more than 157,000 predicted deaths in 2010. Smoking is far and away the most important risk factor for lung cancer. It is evident that risk increases with the number of cigarettes smoked per day and the duration of smoking. Deaths from lung cancer have been decreasing in men since 1990, but have been stable in women since 2003 after continuously rising for several decades. These trends reflect historical differences in smoking between men and women, and the decrease in smoking rates over the past 40 years.

The cancer community is poised to take advantage of the convergence of genetic information, appropriate screening techniques (see section on NLST on page 14), and new targeted therapies for lung cancer. For the enormous number of individuals who will face a diagnosis of lung cancer this year, any brighter outlook is most welcome.

When we say lung cancer, we are actually referring to four different subtypes. Three subtypes are non-small cell lung carcinomas, or NSCLC: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma; the fourth subtype is small cell carcinoma. This first-level classification is likely to be the start of solving a complicated challenge of linking diagnostic characteristics to the most effective treatments. NCI-supported researchers are beginning to uncover genetic drivers of these four subtypes and applying this molecular knowledge for clinical benefit. However, it is clear that the best in diagnostic technologies and therapeutic advances will be needed to make significant progress in treating this very complex collection of diseases. Ideally, this will be complemented by downward trends in smoking rates, which is the most effective way to reduce the burden of lung cancer.

There are currently several mutations that are known to exist in lung cancer, including EGFR and RAS gene mutations in non-small cell lung cancer. Scanning electron micrograph image of a small cancerous tumor inside an alveolus, or air sac, in a lung.
cancer. As with melanoma and some other cancers, BRAF gene mutations have also been found in lung cancers. Last year, researchers identified a genetic target known as a gene translocation, or movement of a gene fragment from one chromosomal location to another. The translocated gene, EML4-ALK—found in 5 percent of NSCLC patients—can be acted on by crizotinib, a promising new drug with minimal side effects. Crizotinib acts by blocking the ALK kinase, believed to promote tumor growth. Results from this phase I trial showed that more than half of treated patients experienced tumor shrinkage while 33 percent had their tumors stabilize. The development of crizotinib was made possible through molecular tumor characterization that was conducted at NCI-designated Cancer Centers. The drug was first tested against anaplastic large-cell lymphoma as well as on neuroblastoma and NSCLC cells grown in the laboratory. Preliminary results of the phase I trial were so promising that a trial testing crizotinib in children with neuroblastoma was launched less than six months after the release of the results (see neuroblastoma profile).

While efforts to further decrease smoking rates are critical, there is also great opportunity to utilize molecular and genetic information to significantly improve the treatment options available to patients diagnosed with lung cancer. This will require continued investigation into the biology of the various types of lung cancer and coordination between laboratory and clinical researchers to optimize existing treatment strategies and develop new ones.

“I think it’s an exciting time now, because if we can influence early diagnosis and prevention of lung cancer, and care of discovered lung cancer, we could actually make a major change to total cancer mortality in the United States. [Already] the total cancer mortality has gone down over the past five to ten years mainly due to decreases in cigarette smoking.”

— John Minna M.D., director of the Harmon Center for Therapeutic Oncology Research at the University of Texas Southwestern Medical Center
In 2010, ovarian cancer was the fifth most common cause of cancer death in U.S. women. Each year more than 21,000 American women are diagnosed with ovarian cancer, and about 14,000 die from the disease, making ovarian cancer the most deadly cancer of the female reproductive tract. Though this cancer is diagnosed in adult women of all ages, the five-year survival rate of 57 percent for women under 65 years of age is nearly twice that of women over 65. Ovarian cancer is particularly devastating because the disease frequently is not recognized until relatively late in its progression, due to the lack of early symptoms and effective screening tests. Currently, fewer than 20 percent of ovarian cancers are diagnosed early, when treatment is most effective. Prognosis is particularly discouraging for patients with advanced-stage disease—only about one-third live five years past their diagnosis.

Although ovarian cancer continues to be a major problem, cancer researchers are making headway in improving diagnosis and treatment as well as advancing our basic understanding of this disease, and NCI is mounting several major efforts to push progress in these areas. For example, the most aggressive type of ovarian cancer was one of the three cancer types analyzed during the pilot phase of The Cancer Genome Atlas. In early studies, significant heterogeneity was observed among the nearly 500 ovarian tumors that underwent molecular characterization. While virtually all of the tumors had mutations in the well-characterized tumor suppressor gene \( p53 \), there were other mutations present in smaller subsets of tumors, including mutations in \( BRCA1 \) and \( BRCA2 \) (genes also associated with hereditary breast cancer).

Another finding from the ovarian cancer characterization has exciting therapeutic potential. There are many DNA copy number changes—large regions of DNA whose number of copies are increased or decreased,
compared with normal DNA—consistent with a high level of genomic instability. There are some indications from studies on ovarian and other types of cancer that it may be possible to exploit genomic instability therapeutically. In addition, there may be recurring patterns to some regions of DNA whose copy number is increased or decreased. Areas of increased copy number found in a high proportion of ovarian cancers are likely to contain one or more oncogenes that contribute to the malignant properties of the cancer. Cancer biologists can analyze the candidate genes that lie within these regions to determine which are the most important for ovarian cancer. This type of analysis may identify new therapeutic targets with relevance to a high proportion of ovarian cancers.

As with all TCGA data, the genomic information is being made freely available to the scientific community, providing opportunity for researchers from different backgrounds and with different perspectives to gain insight into the disease. In one example, the comprehensive molecular analysis carried out by TCGA is being used by systems biologists to develop computational models that aim to predict patient response to various therapeutic interventions based on a tumor’s molecular profile. These and other efforts eventually should help match patients with molecularly diverse ovarian tumors to the most appropriate treatments.

Despite the challenges to treatment of advanced ovarian cancer, some progress is already being made. For example, bevacizumab (see glioblastoma profile) has demonstrated activity in women with recurrent ovarian cancer. In 2010, results from a phase III clinical trial studying the effect of adding bevacizumab to standard chemotherapy treatment in women with newly diagnosed, advanced ovarian cancer, found that addition of the drug extended survival by several months compared to standard chemotherapy alone.

Technological advances in the areas of molecular diagnostics and imaging have potential to facilitate the development of effective and minimally invasive early-detection tests. Through its Early Detection Research Network and other mechanisms, NCI supports translational researchers at institutions across the country who are using varied approaches to identify potential screening biomarkers and conducting the necessary clinical and epidemiological research to confirm promising leads. Much of the work is focused on developing panels of biomarkers that can more accurately detect cancer at an early stage. Some progress is being made in this area, but it is clear that more work is needed to develop tests sufficiently sensitive to detect cancer early enough to improve patient outcomes.
IMMUNOTHERAPY ADVANCES

The pace of progress in immunotherapy has quickened in recent years, with some early-stage clinical trials of different therapies showing positive results for several different cancer types. In a recent large clinical trial, a monoclonal antibody called ipilimumab (also known as MDX-010), which treats cancer by binding to cells of the immune system and inhibiting their activity, became the first immunotherapeutic agent to show an increase in the survival of patients with advanced melanoma whose disease was no longer responding to other treatments. Given the paucity of effective treatments for patients with advanced melanoma, this finding represents a significant therapeutic advance. In late March, the FDA approved that drug, which will be marketed under the name Yervoy, to treat late-stage melanoma.

As of early 2011, there were nine such immunotherapeutic agents that are FDA-approved, including trastuzumab. Many other such agents, for many types of cancers, are being tested in clinical trials.

Immunotherapy using a syringe to remove purified lymphocytes from a blood bag, prior to addition of Interleukin-2 (IL-2).

Other forms of immunotherapy also hold promise. Last year FDA approved the first therapeutic cancer vaccine. Sipuleucel-T (Provenge) is designed for men with advanced prostate cancer. A different therapeutic vaccine developed by NCI investigators to treat advanced prostate cancer is moving into a phase III, or advanced, clinical trial.

Other potentially promising immunotherapy approaches include inducing the immune system to target so-called tumor stem cells—or tumor-initiating cells, which are thought to be a chief cause of cancer recurrences—or to attack normal cells in the tumor microenvironment that cooperate with tumor cells to help them survive and spread to other parts of the body.

Despite the progress we have made, more therapies to effectively stimulate the immune system to destroy cancer cells and promote destruction of tumors are urgently needed. The development of reliable animal models of cancer that more closely mimic how the human immune system responds to tumors will provide invaluable tools for developing future immunotherapy agents and vaccines for cancer.
Finding drugs that kill cancer cells while leaving normal cells unscathed has been a major challenge in cancer treatment. However, there have been considerable advances in genomics in the last decade that have revealed a novel and promising approach: synthetic lethality. The concept is simple—a compound targeting a particular gene or pathway is selectively lethal to cells that harbor a cancer-causing mutation in a complementary pathway. Healthy, noncancerous cells are spared. In this method, two genes are said to be in a synthetic lethal relationship if disruption of either gene alone is not lethal, but changes in both genes—either by mutation or chemical inhibition—causes cell death.

The approach tailored for cancer biology is based on the premise that oncogenic mutations often cause cancer cells to develop secondary dependencies on other genes that are not inherently oncogenic. Chemical inhibitors that disrupt these latter genes result in an oncogene-specific synthetic lethal interaction, and thus cell death. Healthy, noncancerous cells are spared.

As an example, an exciting new class of drugs, called PARP (poly adenosine-disphosphate-ribose polymerase) inhibitors, is being tested in a number of clinical trials in cancer patients with BRCA gene mutations. The BRCA and PARP genes, which have a synthetic lethal relationship, play different, but complementary, roles in DNA repair. Loss of either of these genes allows the cell to survive; but when PARP activity is blocked in cells with BRCA gene mutations, the cells lose their ability to repair themselves, resulting in cell death. Equally important, PARP inhibition, which kills cancer cells, spares cells that have at least one normal copy of the BRCA gene.

Results from a recent phase I study using olaparib, a PARP inhibitor, showed that nearly 60 percent of patients who were BRCA gene mutation carriers and had ovarian cancer, breast, or prostate cancer, had some measure of clinical benefit. More than one-third of patients had tumor shrinkage in phase II studies of olaparib (AZD-2281) conducted in women with BRCA1 or BRCA2 gene mutations and advanced chemotherapy-refractory breast or ovarian cancer. A second PARP inhibitor, iniparib (BSI-201), appears to be even more promising. In combination with conventional chemotherapy, iniparib improved the duration of overall and progression-free survival in women with metastatic triple-negative breast cancer nearly 40 percent compared to those who received chemotherapy alone. Iniparib did not cause additional toxicities.

Cancer patients with BRCA1 and BRCA2 gene mutations are not the only candidates for PARP inhibition therapy. The Cancer Genome Atlas has revealed numerous other tumors with defects in DNA repair, creating opportunities for more types of synthetic lethality-based therapies.

Researchers are also using the concept of synthetic lethality in genome-wide and chemical searches to identify cancer-killing drug combinations and new gene-targets to kill lung cancer cells. An NCI-sponsored study identified 80 new genes that were synthetically lethal in combination with taxol treatment of cancer cells. Inactivation of these genes killed lung cancer cells but not normal cells, and only in the presence of a very low dose of taxol. This type of synthetic lethal approach has enormous potential not only for the treatment of lung cancer but numerous other cancers as well. Through combining novel, synthetic lethal inhibitors with traditional chemotherapeutic drugs, unlimited numbers of genetically diverse cancers could potentially be treated with fewer side effects. These findings seem to have great potential, but they were made in cultured cells, and it has not yet been determined that they accurately predict therapeutic response in people with cancer.
If today’s new understandings of cancer biology are to benefit cancer patients on a broad scale, they must be coupled with a modernized system for conducting cancer clinical trials. This system must enable clinical researchers across the nation to acquire tumor specimens and conduct genetic tests on each patient, to efficiently sequence the DNA from those samples, to manage and secure vast quantities of genetic and clinical data, and to identify subsets of patients with tumors that demonstrate changes in specific molecular pathways—pathways that can be targeted by a new generation of cancer therapies. And all of this must be done one patient at a time.

As part of its effort to transform the cancer clinical trials system, NCI asked the Institute of Medicine (IOM) in 2009 to review the Clinical Trials Cooperative Group Program. This program involves a national network of 14,000 investigators currently organized into nine adult Cooperative Groups and one pediatric cooperative group that conduct large-scale cancer clinical trials at 3,100 sites across the U.S. The IOM report, issued in April 2010, noted that the current trials system—established a half-century ago—is inefficient, cumbersome, under-funded, and overly complex. Among a series of recommendations, the report urged that the existing adult cooperative groups be consolidated into a smaller number of groups, each with greater capabilities and the ability to function with the others in a more integrated manner.
In December 2010, NCI announced its intent to begin consolidating the current nine adult cooperative groups into up to four state-of-the-art entities that will design and perform improved trials of cancer treatments, as well as explore methods of cancer prevention and early detection and study quality-of-life issues and rehabilitation during and after treatment. The sole pediatric cooperative group was created by consolidating four pediatric cooperative groups a number of years ago, and that group will not be affected by the current consolidation effort.

NCI also intends to consolidate nine existing tumor banks into three to give researchers improved access to a nationally integrated tissue resource. Currently, optimal use of tissue specimens from NCI-supported prospective trials is impeded by the lack of a national IT system for locating tissue, the lack of standard operating procedures, and the lack of a transparent process to prioritize the distribution of specimens on a national scale.

Revitalizing a cancer clinical trials system must enable researchers across the nation to acquire tumor specimens and conduct genetic tests on each patient, efficiently sequence DNA, and identify subsets of patients with tumors that demonstrate changes in specific molecular pathways.

The consolidation of the cooperative groups is also intended to improve the efficiencies of operations centers and data management centers, and to facilitate the training of investigators in applying molecularly based approaches to large-scale clinical trials. In addition, NCI envisions using the Cooperative Group Program as a means for preparing the oncology community, including community physicians, for the widespread introduction of molecularly-based therapies.

The consolidation of the Cooperative Group Program is the most recent in a series of changes initiated by NCI, through its Division of Cancer Treatment and Diagnosis and the Coordinating Center for Clinical Trials, to revitalize the nation’s cancer clinical trials system. Other transformative changes introduced in recent years include those outlined in a working group report which can be found at http://ccct.cancer.gov/files/OEWG-Report.pdf:

- Reduce by half the time to initiate new clinical studies and terminate studies not begun within 18 to 24 months of concept approval.
- Revamp the prioritization process for large phase II and phase III treatment trials by creating disease-specific and modality-specific steering committees.
- Improve the use and efficiency of the NCI Central Institutional Review Board, which reduced the average time for final sign-off on protocols for national trials from 150 days in 2007 to 42 days in 2010.
- Increase reimbursement to clinical trials sites.
was sworn in as the new Director of the National Cancer Institute just nine months ago, so this is the first time that I have been privileged to voice my pride in NCI’s past accomplishments and the promise of future achievements in its annual report on budget needs and priorities.

Although I am new to this position, I am not new to cancer research or to the NCI. I received my scientific training here more than 40 years ago, started to work on cancer-causing viruses shortly thereafter, and have been supported by NCI funds throughout my career. In these intervening years, I have witnessed profound changes in our knowledge about the biology of cancer. When I began to study animal models of cancer in the early 1970s, the collective understanding of the origins and progression of cancer was negligible; now we are able to describe such events in minute detail at the molecular level. This transformation has been accompanied by gradual—and occasionally dramatic—improvements in the control of human cancer. In an increasing number of cancers, new concepts about the biology of cancer are now driving beneficial changes in the ways we prevent, diagnose, and treat disease.

The importance of the NCI throughout this rich history can best be appreciated by considering the amazing diversity of the approaches it has undertaken to control cancer—through basic research on normal cells, genes, and proteins; through studies of the pathogenesis of various forms of cancer; and through efforts to improve the prevention, diagnosis, and treatment of cancers.

In the first half of this report, we have tried to convey the depth of these enterprises, while emphasizing at least three big ideas. First, cancer constitutes a complex set of diseases. It is not simply one disease that happens to afflict many organs of the body; it is, instead, many different disorders that display some common themes, including mutations in many important genes, alterations in essential cell functions, and novel interactions with the cellular environment in which tumors grow. Second, cancers can be controlled in many different ways. As reflected in their biological complexity, cancers invite several strategies to improve control. These include a number of approaches to prevention, multiple methods to screen for early stages of carcinogenesis, more precise diagnostic tests, and better
therapies. The improved treatments are based on knowledge of specific genetic changes in cancer cells, the functions of the immune system, the susceptibilities of cancer cells to various drugs and radiotherapy, and an understanding of the symptoms and complications of these diseases.

Third, advances against cancer that benefit people depend on science of many kinds. Progress in the control of cancer has required new knowledge from the many fields of research that the NCI supports—from molecular and cell biology, genetics, virology, immunology, and chemistry; from animal models of cancer; from the behavior and biology of human beings; and from many other directions. In brief, cancer represents one of the greatest challenges to the strength of modern medical science.

My colleagues and I have chosen to illustrate these ideas, and the complexity they embody, by describing recent progress made against six kinds of cancer, chosen somewhat arbitrarily from a much larger repertoire of successes. We acknowledge that none of these six stories is over; in all situations, we have much more to do. But each narrative reveals a promising path to further progress.

The men and women who have achieved these successes and who are poised to extend them represent our greatest resource. With the additional funds requested here, their ambitions and talents can be unleashed, ensuring that the NCI can take the greatest possible advantage of the opportunities created by its remarkable history.

Harold Varmus, M.D.
Director, National Cancer Institute
This budget request consists of two components: the increase required to maintain our present level of operations (current services) and the increase required to initiate new initiatives and expand existing ones.

It should be noted that we have carefully reviewed our current expenditures and have found important efficiencies and savings. The current services increase is the amount that will be required to sustain NCI programs, restore some of the funding cuts that have been implemented over the past several fiscal years, and provide for some minimal growth. Noncompeting Research Project Grants (RPGs) would be funded at committed levels, the number of competing RPGs would be maintained at the FY 2010 level, and most other mechanisms would receive sufficient increases to cover cost of living adjustments based on the Biomedical Research and Development Price Index (BRDPI). This budget level also includes funds to make critically needed capital repairs and improvements at the NCI-Frederick Federally Funded Research and Development Center.

The additional funds requested reflect the Institute’s assessment of where more funding will make the greatest difference in reducing cancer incidence and mortality. Together, with growing the research grants portfolio, these new or expanded initiatives—cancer genomics, transformation of the clinical trials system, and more effective translation of research results to clinical utility—offer the greatest current hope of advances against cancer.

### National Cancer Institute

#### At a Glance (dollars in thousands)

<table>
<thead>
<tr>
<th>Description</th>
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<tr>
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