THE NATIONAL CANCER INSTITUTE

The Nation's Investment in Cancer Research

A Budget Proposal For Fiscal Year 1999

Prepared by the Director
National Cancer Institute

National Institutes of Health

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Director's Message

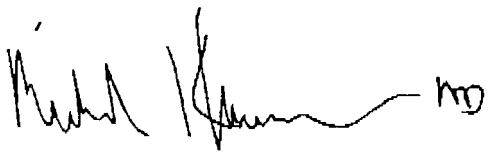
We live in an era of astounding scientific discovery — discovery that has given us dramatic new insights into the fundamental processes of cellular development, maintenance, and proliferation and how these processes can be corrupted to cause cancer. Equally as important, we are finding new ways to apply what we have learned to prevent, detect, and treat cancer. Our hard work has begun to bear tangible fruit: The Nation's death rate from cancer fell between 1991 and 1995 — the first sustained decline since we began keeping records in the 1930s. In human terms, this means that, this year alone, thanks to remarkable advances in cancer prevention, detection, and treatment, 10,000 to 15,000 men, women, and children with cancer who may not have survived 10 years ago now have a real chance at living long, full, and productive lives.

But our excitement at this progress must be tempered by the fact that cancer, and its associated human suffering and death, remain all too common. Nearly half of us will develop cancer; over one in five of us will die from cancer. Within five years, cancer will be the leading cause of death in the United States, responsible for over eight million years of life lost prematurely each year.

How can we build on the unprecedented successes of our recent accomplishments to reduce the burden of cancer, or even eliminate it from our lives? First, we must sustain the proven research programs that have enabled us to come this far. At the National Cancer Institute (NCI), we have created an infrastructure that promotes discovery, attracted some of the best scientific minds to the cancer problem, and initiated ground-breaking programs that have yielded critical knowledge, improved patient care, and saved lives. We must continue to offer these programs the full measure of our support. At the same time, we must be quick to seize extraordinary opportunities to further progress brought about by our previous research successes. And we must ensure that the full promise of our research findings is realized by creating and sustaining mechanisms that will enable us to rapidly translate our findings from the laboratory into practical applications that will benefit everyone.

The Congress has requested that the Director of the National Cancer Institute prepare a budget estimate for cancer research. This document presents that estimate for Fiscal Year 1999. The following pages identify the resources needed to sustain current successful efforts. In addition, we describe four areas of unprecedented cancer research opportunity which, if exploited, will greatly increase our capacity to reduce suffering due to cancer. Finally, we describe the steps we need to take to meet the challenge of bridging the gap between the discovery process and practical application — to convert our knowledge of cancer into advances in prevention, detection, diagnosis, and treatment.

In the past two years, we have made tremendous progress against cancer. The decrease in the cancer death rate is an important step forward. However, there is much to learn, and much more to do. This budget represents the investment needed to take the next crucial steps toward the ultimate goal of fully eradicating cancer from the lives of all people. It is an investment in hope — the hope that springs from knowing that science is leading us inexorably toward the day when cancer is conquered.



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Executive Summary

The ultimate goal of the National Cancer Institute (NCI) is to prevent or cure cancer. As we approach the 21st century, we have cause for celebration tempered by the knowledge that we still have much to do to achieve our goal. We celebrate a long-awaited turning point, the drop in the cancer death rate between 1991 and 1995, the first sustained drop of its kind since national record keeping was instituted in the 1930s. However, though our knowledge of cancer is ever increasing, we still do not fully understand the cause of cancer — an understanding that is the keystone of further progress. It is at this critical juncture of increasing knowledge and decreasing mortality that we must press forward with tremendous energy and increased resources to continue the NCI's vital and lifesaving work.

In order to achieve our goal, NCI envisions a three-pronged approach:

1. Sustain at full measure the proven research programs that have enabled us to come this far.
2. Seize extraordinary opportunities to further progress made possible by our previous research discoveries.
3. Create and sustain mechanisms that will enable us to rapidly translate our findings from the laboratory into practical applications that will benefit everyone.

Sustain at full measure the proven research programs that have enabled us to come this far.

The heart of NCI's research efforts rest in its Infrastructure for Discovery (see p. 31). This is the underpinning for activities that encompass all aspects of cancer prevention, diagnosis, treatment, and control. Each year, the efforts of thousands of scientists in the extramural and intramural communities yield scientific advances in cancer biology, risk, interventions, and control (see Highlights of Progress, p. 9). Our infrastructure supports basic, translational, and clinical cancer research, as well as investment in new research programs to address the needs of cancer patients and survivors, cancer centers, community-based clinical oncology programs and specialized programs of research excellence, training and education opportunities, and communicating research results to our constituents.

Seize extraordinary opportunities to further progress brought about by our previous successes.

In 1996, NCI began a process of looking critically at the field of cancer research and identifying areas of discovery with exceptional promise for achieving pivotal advances both in our knowledge of cancer and in benefits for patients and those at risk for cancer. We identified four Extraordinary Opportunities as being ripe for investment.

Cancer Genetics

Identify every major human gene predisposing to cancer; use the knowledge we gain as we identify these genes to help patients at risk; and deal with the psychosocial, ethical, and legal issues associated with inherited cancer susceptibility.

Preclinical Models of Cancer
Create animal models of human cancers; build the experimental foundation to use these models effectively; and develop the infrastructure and procedures needed to make these models available to all researchers.

Imaging Technologies
Discover and develop techniques that will further increase the precision, accuracy, and scope of imaging diagnosis; and integrate imaging further into the practice of clinical oncology.

Defining the Signatures of Cancer Cells: Detection and Diagnosis
Develop new methods for detecting tumors at their earliest stages, when the number of tumor cells is small and the chance for cure or control is greatest; establish methods for detecting changes in cells that accompany and determine the development of cancer to enable the generation of new prevention strategies and tools. Create a new approach to accurate diagnosis that will allow us to tailor therapy to each distinct cancer and target a new generation of therapeutics to the particular changes that occur in the development of each cancer.

Create and sustain mechanisms that will enable us to rapidly translate our findings from the laboratory into practical applications that will benefit everyone.

How will we convert our knowledge of cancer into advances in prevention and care on the scale that is needed to conquer cancer? To meet this challenge, we must have a research base that can bring the best of our developing knowledge — the best ideas, technologies, and people — to the problems of cancer prevention and care. Response to this challenge requires increased investment in seven key areas:

National Clinical Trials Program
We need to create a clinical trials program that can test the most new ideas about prevention, detection and treatment of cancer in the shortest possible time. We need to ensure that all people who wish to participate in a clinical trial are able to do so.

Investigator-Initiated Research
We need to fund the top 40 percent of research grants to ensure that excellent ideas have the chance to be tested, whether they are in basic, clinical, or population research, or the translational research that links them. We need to ensure that new investigators are attracted to cancer research.

Support for Clinical Investigators
We must create and maintain an environment that supports and encourages health care professionals who are involved in clinical research.

Cancer Centers: Restructuring and Expansion
The Cancer Centers program should grow over the next few years to include about 75 institutions and broaden its scope to include smaller organizational units that can respond efficiently to highly specialized areas of opportunity, and perform the translational research so critical to move from laboratory insights to clinical testing.

Informatics and Information Flow
We must develop a Cancer Informatics Infrastructure that will lower the barriers for patients, families, at-risk individuals, and physicians to learn about available clinical trials, and to create an infrastructure that facilitates information exchange among researchers, clinicians, and the public.

Studying Emerging Trends in Cancer
We must ensure that the Surveillance, Epidemiology, and End Results (SEER) database not only tracks accurately changes in cancer incidence and survival, but also contains information that will enable researchers to generate hypotheses and answer questions about the basis of observed changes in trends over time.

Training and Education
We must take steps now to ensure that some of the brightest, most creative young people from every segment of the American population enter the cancer research field. We must convince some of them that the field of translational research offers tremendous challenges and rewards.

In summary, because such a large commitment cannot be made without a full understanding of the infrastructure, programs, and research to be supported, the National Cancer Institute has prepared this document to provide a concise yet comprehensive view of NCI's Research Programs and Infrastructure for Discovery, our investment plan for Extraordinary Research Opportunities, and our plan to meet the future challenge of bringing discoveries to practical application for the benefit of people. The cancer research enterprise involves not only futuristic research but also exciting efforts that will soon yield results, as discussed in the "Immediate Opportunity" and "On the Cutting Edge" boxes throughout the document. Finally, "People's Stories" throughout the document remind us that the research we support, whether it yields outcomes immediately or in the future, is conducted with a single purpose: to help people with cancer, or who are at risk for cancer, and to remove the shadow of cancer from the lives of all Americans.

In order for the National Cancer Institute to sustain our current research investment, identify and invest in new research opportunities, and anticipate our future challenges and invest in them now, we request the following funding.

1999 Bypass Budget Request

1. **Sustaining ongoing research programs:**

   TOTAL: $2.58 billion

2. **Seizing extraordinary opportunities for further progress brought about by our previous successes:**

   Cancer Genetics: $53.7 million

   Preclinical Models of Cancer: $29.3 million

   Imaging Technologies: $39.0 million

   Defining the Signatures of Cancer Cells: $63.5 million

   TOTAL: $185.5 million

3. **Creating and sustaining mechanisms that will enable us to rapidly translate our findings from the laboratory into practical applications:**

   National Clinical Trials Program: $170.0 million

   Investigator-Initiated Research: $40.4 million

   Support for Clinical Investigators: $66.0 million

   Cancer Centers — Restructuring and Expansion: $70.0 million

   Informatics and Information Flow: $20.0 million

   Studying Emerging Trends in Cancer: $25.0 million

   Training and Education: $34.1 million

   TOTAL: $425.5 million

GRAND TOTAL: $3.191 billion

Highlights of Progress 1996-1997

Inside...

- Scientists who discovered the gene for Gorlin syndrome, an inherited disease that predisposes individuals to basal cell carcinoma of the skin (BCC) and to congenital skeletal defects, discovered a surprising fact about that gene. Now, we're well on our way to understanding how that gene works in humans, which could speed the development of new treatments for BCC, the most common cancer in humans. See page 28.
- An ambitious new venture will enable researchers to recognize all major steps of tumor development at the molecular level. See page 66, or visit the Cancer Genome Anatomy Project web site at http://www.ncbi.nlm.nih.gov/ncicgap.
- Prostate surgeons find that practice makes perfect as new technology enables them to perform a computer-assisted "dress rehearsal" of a prostatectomy before the actual surgery takes place. See page 60.

Scientific Highlights

Cancer Death Rate Declines. The percentage of the U.S. population that dies from cancer each year fell between 1991 and 1995, the first sustained decline since national record-keeping was instituted in the 1930s. This encouraging trend is attributable in large measure to a decrease in smoking rates, although better early detection methods and advances in treatment have likely played a significant role. See page 12.

Breast Cancer Genetics. In a study of over 5,300 Ashkenazi Jewish individuals (Jews of Eastern European descent) in the Washington, D.C. area, scientists found that three specific alterations in the breast cancer genes *BRCA1* and *BRCA2* are associated with an increased risk of breast and ovarian cancers, but that the risk for these cancers, while higher than that of the general population, was lower than most previous estimates. On average, women carrying one of the three alterations have a 56 percent chance of getting breast cancer by age 70 (compared with a 13 percent chance for non-carriers) and a 16 percent chance of getting ovarian cancer (compared with 1.6 percent for non-carriers).

Prostate Cancer Genetics. The D.C.- area Ashkenazi study (above) also assessed prostate cancer risk for men carrying *BRCA1* and/or *BRCA2* alterations. Scientists estimated that men with one of the alterations have a 16 percent chance of getting prostate cancer by age 70, compared with 3.8 percent for non-carriers. In a separate study, scientists narrowed down the location for the first prostate cancer gene *HPC1,* to the long arm of chromosome 1. It is estimated that one in 500 men carry an altered version of *HPC1*. The gene itself, once identified, is expected to provide insight into the cause and progression of both the hereditary and sporadic forms of prostate cancer, and suggest strategies for prevention and treatment of this very common malignancy. See p. 30 for more on prostate cancer.

HPV Vaccine. Cervical cancer is the leading cause of genital tract cancer deaths world-wide. Sexually transmitted human papillomaviruses (HPV) are associated with 90 percent of cervical cancers, but there is not currently an effective treatment for HPV infection. However, NCI researchers are preparing to launch a pilot field study to test the effectiveness of a vaccine they created to prevent HPV infection, and Phase I trials are set to begin soon to test the vaccine's safety. See p. 17.

Breast Cancer Prevention Trial. Recruitment for the Breast Cancer Prevention Trial, the first large-scale, randomized study to assess whether a five-year course of the breast cancer treatment drug tamoxifen (Nolvadex®) can prevent breast cancer in women at increased risk, ended in May 1997. The results of this trial are expected in two to three years. The trial will follow 13,000 women at increased risk of breast cancer, as determined by age or personal or family medical history.

Laser Capture Microdissection. A powerful new technique known as Laser Capture Microdissection (LCM), developed by a team of researchers from NCI and the NIH's National Center for Research Resources, allows a doctor to extract cells of interest from a tissue sample with the click of a button. LCM will replace the tedious and inefficient processes needed until now to diagnose cancer or study patterns of gene expression in various cell types. See page 66.

Treatment Advances

Breast Cancer. Chemotherapy prior to surgery for breast cancer can shrink the tumor significantly — so much so that some women who would otherwise require a mastectomy may instead undergo a lumpectomy. In a study by the NCI-supported National Surgical Adjuvant Breast and Bowel Project, investigators found that women with palpable breast cancers who had preoperative chemotherapy were nearly three times more likely than women who had not (22 percent versus eight percent) to be able to avoid mastectomy and undergo less disfiguring lumpectomy. See page 39.

Prostate Cancer. NCI-supported researchers found that hormone therapy after radiation therapy can prolong disease-free survival and perhaps overall survival of patients with locally advanced prostate cancer. Although hormone therapy is known to be an effective treatment for metastatic prostate cancer, its use had not been assessed in combination with radiation for initial treatment of locally advanced disease.

Melanoma. The use of interferon alpha-2b (IFN alpha-2b) as adjuvant therapy following surgery for malignant melanoma prolongs both relapse-free and overall survival in patients at high risk of recurrence, making it the first agent to show a significant benefit as an adjunct to surgery. NCI supported researchers found that IFN alpha-2b resulted in a 42 percent increase in the number of people achieving relapse-free survivial five years after treatment.

Nasopharyngeal Cancer. Chemotherapy and radiation therapy have both been proven to be useful treatments against nasopharyngeal cancer — and a new study indicates that together, they're even more powerful. NCI Cooperative Group researchers evaluated radiation therapy alone versus combined chemotherapy and radiation therapy for treatment of nasopharyngeal cancer and found that the combined therapies improved two-year survival rates from 55 percent to 80 percent.

NCI Highlights

New Offices. Several new offices have been formed to facilitate communication and partnership with our constituents. These offices include the Office of Special Populations Research, the Office of Liaison Activities, and the Office of Cancer Survivorship. For more information, see page 25.

Program Reviews. NCI has completed in-depth reviews of its Cancer Centers and Prevention programs. See page 27. These reviews have resulted in far-reaching organizational and operational changes. In addition, reviews of the Cancer Control and Clinical Trials programs are ongoing; results are expected in fall 1997.

Reorganization. The 1995 Bishop-Calabresi Report evaluated the NCI's intramural program, identifying strengths and weaknesses and recommending changes where appropriate. A major recommendation was the complete organizational separation of intramural and extramural programs. As a result of these recommendations, a new

position, that of Deputy Director for Extramural Science, was created; the new Deputy Director is responsible for oversight, integration, coordination, and enhanced communication across the Institute's extramural programs.

In addition, two new extramural divisions, the Division of Cancer Prevention (DCP) and the Division of Cancer Control and Population Science (DCCPS), were created. The DCP will bring added visibility, prominence, and strength to the NCI's prevention programs. The DCCPS will be the new focus for NCI-sponsored research programs aimed at studies in populations, behavior, surveillance, special populations, outcomes, and other aspects of cancer control. It will be created from cancer control programs currently within the NCI's Division of Cancer Prevention and Control, which will be abolished, and the extramural portions of NCI's Division of Cancer Epidemiology and Genetics. The Office of Cancer Survivorship will also be part of the DCCPS.

Introduction

We measure progress against cancer two ways: by our ability to reduce the individual and national burden of cancer, and by the growth of knowledge about cancer. Over the past few years, our knowledge of cancer has grown exponentially, but there is still much we do not know. Only a solid, sustained program of research and discovery will provide us with the information we need to prevent cancer, cure cancer, and manage disease effectively in those we cannot cure. Our success will be measured in terms of fewer deaths, fewer new cases, increased life expectancy, and improved quality of life for cancer survivors.

The 1990s may be remembered as the decade when we measurably turned the tide against certain cancers. After rising throughout the 1970s and 1980s, the overall cancer death rate fell between 1991 and 1995 — a real and promising trend that translates into thousands of lives saved. Most of the improvements in mortality rates are in patients below the age of 65 and in men rather than women. For several malignancies — children's cancers, breast cancer, colon and rectal cancers, Hodgkin's disease, and testicular cancer — decreasing death rates reflect cumulative research successes over the past 25 years.

In addition to reducing mortality rates for many malignancies, we have achieved important improvements in the quality of life for cancer survivors through less disfiguring and less damaging surgical procedures, better pain control, and more effective medication for the side effects of cancer therapy.

After a formidable battle to reduce the prevalence of cigarette smoking, lung cancer rates for men have declined. Lung cancer rates for women, however, continue to rise. For other cancers, including non-Hodgkin's lymphomas, multiple myeloma, melanoma of the skin, and esophageal, brain, and kidney cancers, mortality rates have not fallen or are increasing. And although the overall cancer mortality rate among African Americans is declining, it is still disturbingly higher than the overall mortality rate for other population groups.

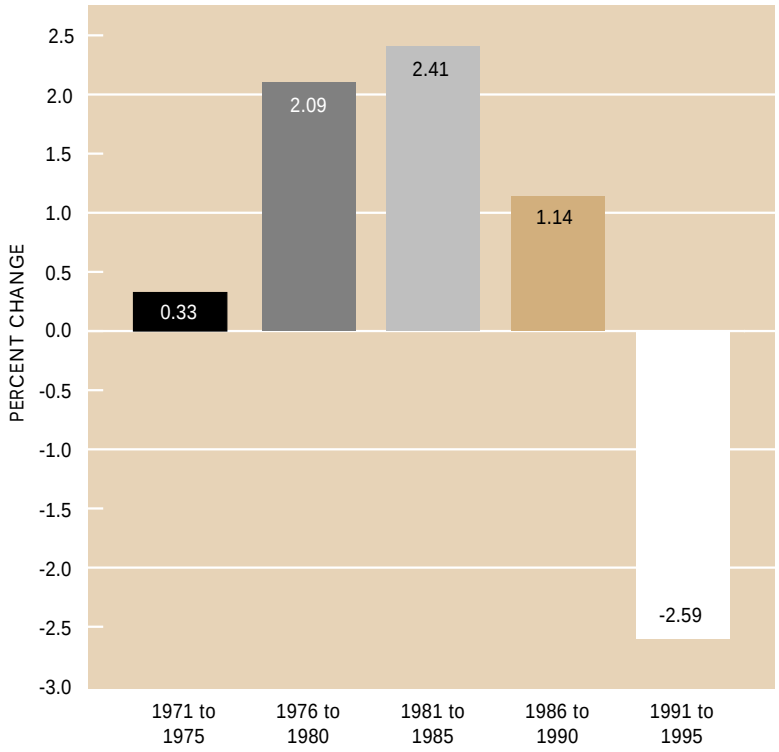
Even taking into account our advances that increase the chances of being cured of many cancers, the number of new cancer cases continues to increase, emphasizing the formidable task ahead. The goal of a reduced cancer burden can only be achieved by the successful translation of discoveries to the benefit of all people who are at risk for and who have cancer.

What is Cancer?

Cancer is a group of diseases that occur when cells become abnormal, dividing and forming more cells without control or order. For cancer to occur, a series of changes in genes that control cell growth and behavior must take place. A critical question in cancer research is how and why these genetic errors occur, and just as important, why the errors are not corrected by the cell's normally efficient surveillance mechanisms.

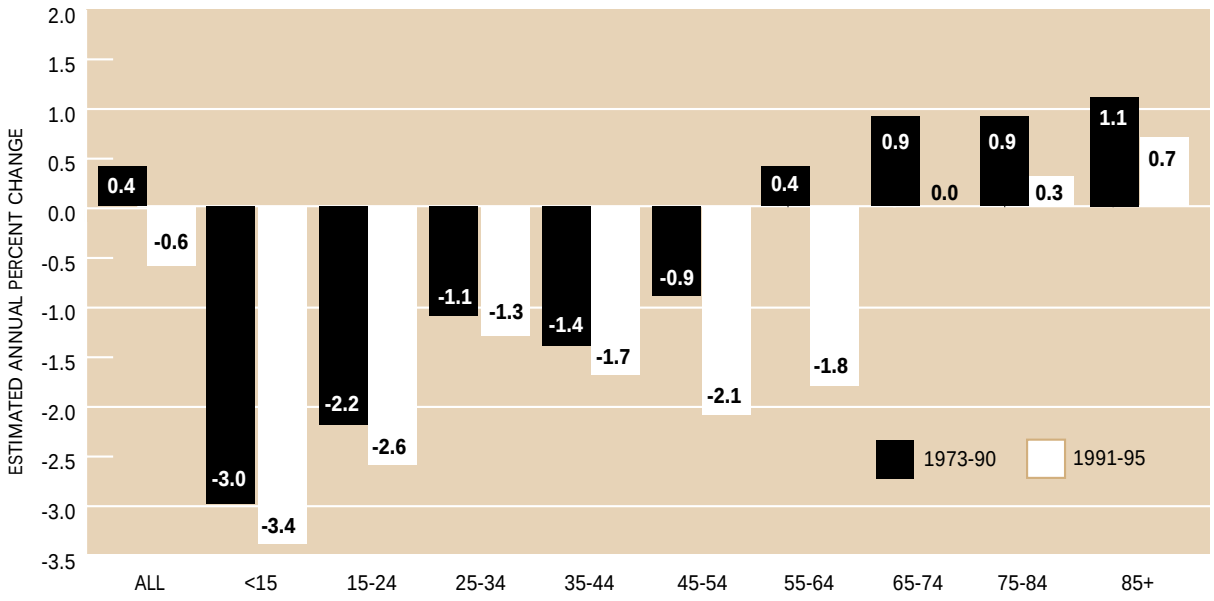
Some people have inherited certain genes that predispose them to get cancer; others get cancer seemingly at random. Ultimately, cancer's origins lie in the interplay between the vulnerability of our genetic material, DNA, and the challenges and stresses that environment — including behaviors such as smoking and dietary habits — places on the cells in which DNA is housed.

Percent Change in U.S. Cancer Mortality Rates for Each 5-year Period, 1971-1995



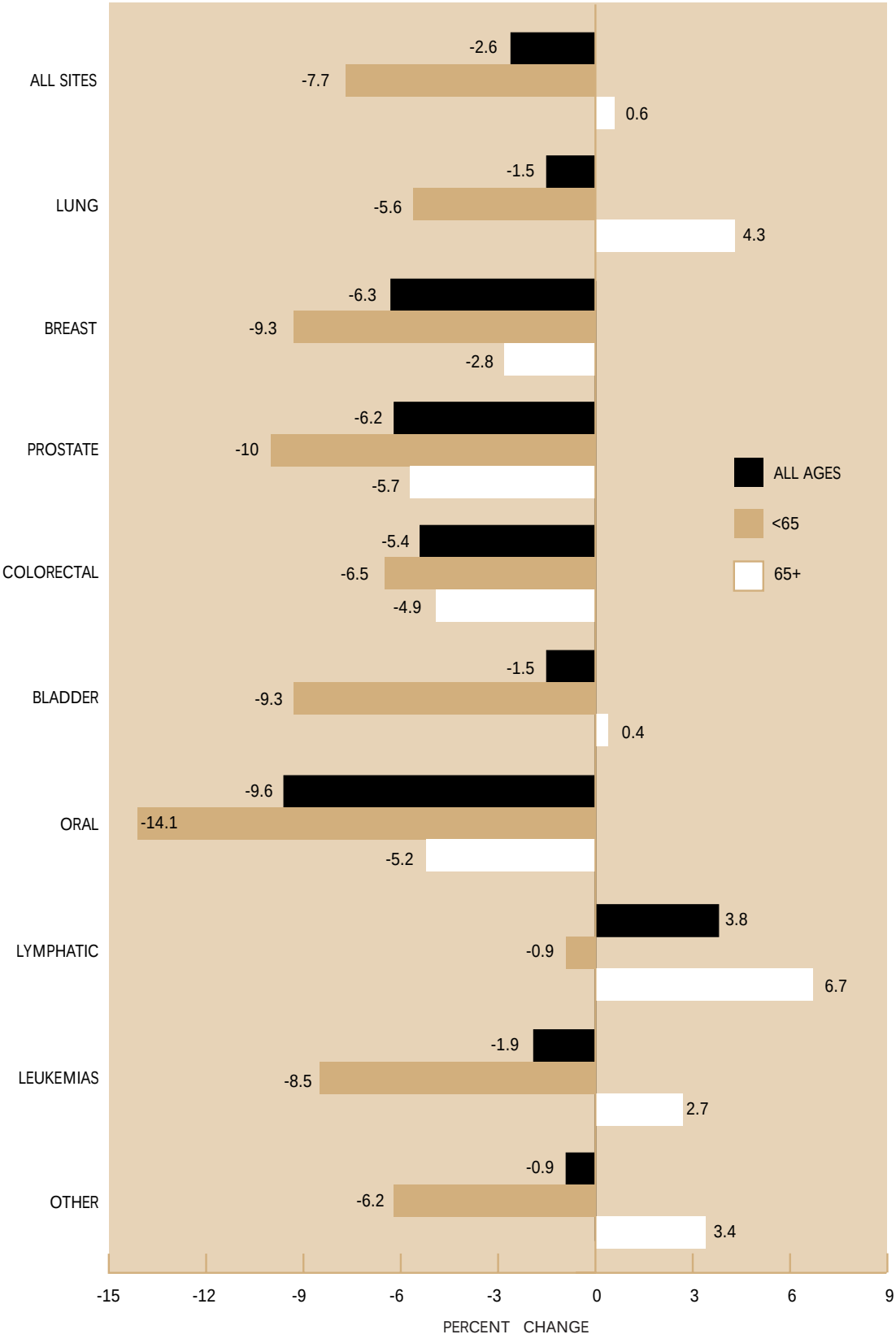
Source: NCHS public use tapes, 1995 preliminary data

U.S. Cancer Mortality, Estimated Annual Percent Change 1973-1990 vs. 1991-1995, All Sites by Age



Source: NCHS public use tapes, 1995 preliminary data

U.S. Cancer Mortality, Percent Change 1991-1995
Both Males and Females, by Age



Source: NCHS public use tapes, 1995 preliminary data

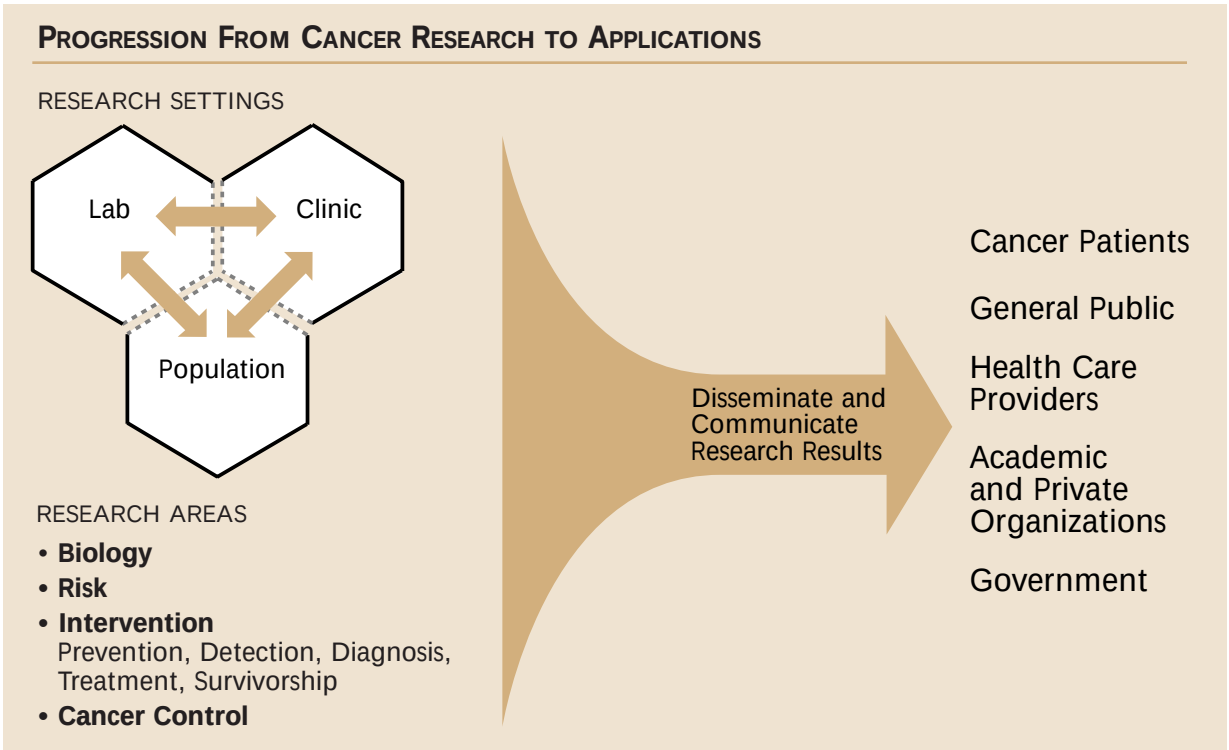
The NCI's Research Programs

Research Settings

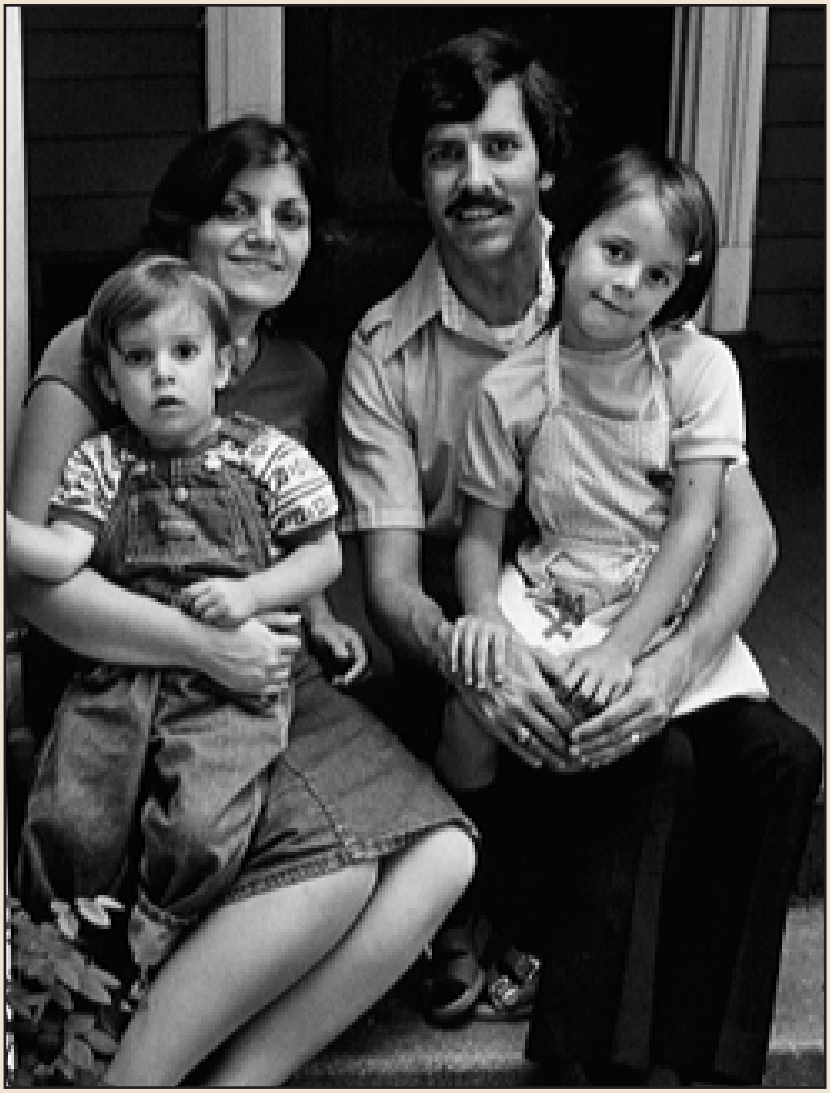
The NCI conducts three classes of research: laboratory, clinic, and population. In the laboratory, research is pursued on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, research is carried out on cancer prevention, detection, diagnosis, treatment, and rehabilitation. In the population, research focuses on the causes, risks, predispositions, incidence, and behavioral aspects of cancer. As the diagram indicates, these three settings influence one another. For example, population-based research on the effects of exposure to a potential cancer-causing agent links to the laboratory where an understanding of the agent's effect on the cell can be explored. Through these linkages, we have identified a sexually transmitted papillomavirus as a primary cause of cervical cancer and subsequently explained why only certain viral subtypes are cancer-causing. Similarly, we have established the relationship between asbestos and mesotheliomas; between reproductive variables such as late menopause and breast cancer; and between dietary factors and a variety of cancers.

Likewise, population-based research on cancer-prone families has led to the isolation of specific genes responsible for inherited cancer syndromes. Specific genetic pathways in cells identified in the laboratory then can be used to predict the course of a patient's disease and his or her response to therapy, or to find ways to detect these cancers very early in their development.

The diagram shows a progression from the results of research through dissemination to application. Research results must be communicated to those who ultimately apply these results in health care and disease prevention settings.



Von Hippel-Lindau (VHL) Disease



There's been so much cancer in our family. The earliest case anyone remembers is my great-grandfather, who had kidney cancer. Other family members have had kidney cancer too, but also spinal, brain, and adrenal gland tumors. Until we joined a family study and found out the cause was von Hippel-Lindau disease, we all felt so helpless, as if it was some kind of family curse.

Von Hippel-Lindau (VHL) disease is an inherited disorder that affects one in 32,000 people worldwide. Adults with VHL have frequent recurrent tumors, primarily in the kidneys, retinas, and the central nervous system. VHL disease is caused by mutations in the *VHL* tumor suppressor gene, first identified by NCI-supported researchers in 1993. Since then, we have discovered that this gene is active throughout the body. The *VHL* gene is long, and it is susceptible to mutations at many different points along its length, resulting in different types of tumors. The mutated *VHL* gene is also implicated in many sporadic (not inherited) cases of kidney cancer.

First-degree relatives of individuals with VHL disease have a 50 percent chance of developing it themselves. With current technologies, genetic testing generally finds about 85 percent of the mutations in families. Screening provides an early warning system for adults who may have the altered gene but no symptoms, and for their children.

There's no cure yet for VHL disease, but we're being monitored regularly now, to catch any tumors early. We know what to look for, and treatments are improving. It's still difficult, of course, but we feel much more hopeful.

Improved imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) scans are enabling earlier detection and better management of VHL-related tumors. For example, earlier detection and treatment of central nervous system tumors are reducing the neurological disabilities that can accompany these cancers. Kidney-sparing surgery with careful follow-up is now the preferred method of managing kidney cancers in VHL patients.

NCI researchers also report progress toward understanding and combating VHL disease. According to a scientist working on VHL:

> "We suspect that at least one job of the normal *VHL* gene is to regulate which genes in cells throughout the body are turned "on" or "off." We are looking for "partner genes" or other factors that, in addition to a mutated *VHL* gene, are necessary for VHL cancers to develop. Some researchers are working to find drugs that will mimic key activities of the normal VHL protein, neutralizing the effects of the defective protein produced by the mutated *VHL* gene. Other investigators are seeking a way to prevent the extensive network of blood vessels that typically develop to feed VHL tumors. A particularly exciting finding is that reintroducing a normal version of the *VHL* gene into kidney cancer cells will prevent them from forming tumors in mice. These are all very promising developments for VHL families."

Research Goals

There are four fundamental goals of cancer research: understanding cancer biology; identifying who is at risk for cancer and why; developing interventions to prevent, detect, diagnose, treat, and enhance survivorship from cancer; and translating research discoveries to the public and to medical practice.

Cancer Biology

The most remarkable progress in the past 25 years has been in our knowledge of cancer biology. We are dramatically extending our understanding of what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously, released from the controls that constrain the replication of normal cells. This transformation results from changes in the function and activity of genes, which are segments of DNA containing the information that directs a cell to make a particular protein product. Of the 100,000 genes found in the human genome, the altered activities of only a small number of genes are responsible for transforming a normal, well-behaved cell — whether in the breast, brain, blood, colon, prostate, or other organ — into a cancer cell. Identifying these "cancer genes" defines the central scientific hunt in cancer biology, and opens an unprecedented window into the nature of cancer.

We now realize that many processes are dysregulated in cancer cells. For example, cancer cells often lose their normal primary function and start behaving like rapidly growing embryonic cells rather than fully mature skin or liver or breast cells, in which growth is slow and regulated. They replicate without regard to the signals that normally indicate when it is appropriate to divide. These cells have damaged mechanisms for repairing DNA errors and often have even lost the fail-safe mechanisms that normally eliminate highly damaged cells. DNA changes can occur due to chemicals, viruses, radiation, and mistakes made each day in the course of duplicating three billion units of DNA each time a cell divides. DNA is very vulnerable to damage, but each cell has the remarkable ability to recognize damage and correct it. When a normal cell recognizes DNA damage, it stops the process of growth and division called the cell cycle. A normal cell either repairs its damage or, if it fails, undergoes programmed cell death (apoptosis). In cancer, these checkpoint controls are lost and the cell continues to divide, transmitting its damaged DNA to its descendants.

No one genetic alteration, however, is enough to make a normal, healthy cell a cancer cell. Rather, an accumulation of changes in a relatively small number of genes during the lifetime of a cell is required. We have learned that some individuals carry a very high lifetime risk of developing cancer because fewer successive changes in DNA are required to take place in one of the trillions of cells in their bodies to transform that cell into a

IMMEDIATE OPPORTUNITY

Cervical Cancer Vaccine

Each year, nearly 16,000 women in the United States are diagnosed with cervical cancer, and more than 4,500 women die from this disease. In developing nations, cervical cancer incidence and death rates are much higher, making it the number one cause of genital tract cancer deaths in the world. Sexually transmitted human papillomaviruses (HPV) are associated with 90 percent of cervical cancers, and young, sexually active women are at highest risk for infection. Currently, there is no effective treatment for infection with HPV. However, NCI researchers are preparing to launch a pilot field study to test the effectiveness of a vaccine they created to prevent HPV infection, and Phase I trials will begin soon to test the safety of the vaccine.

People can be infected with numerous types of HPV, but more than 50 percent of cervical tumors contain one type of high-risk HPV (HPV-16), and another 30 percent contain three other HPV types. Thus, the researchers have developed a vaccine using bits of virus-like particles (VLP) composed of a major structural papillomavirus protein from each of these four HPV-types. They hope that the initial studies will show that the vaccine protects against these four HPV types and will prevent more than 80 percent of cervical cancers. Such a vaccine could provide a critical tool in the fight against cervical cancer, with the potential to save thousands of lives and millions of dollars in screening and other health care costs each year.

Genetic Counseling Directory Available on the Web

"The Familial Cancer Risk Counseling and Genetic Testing Directory" is a searchable database with the names of more than 200 health care professionals who take referrals for cancer genetics education and counseling. The directory is located on the CancerNet™ Web site, operated by NCI's International Cancer Information Center, and is searchable by name, city, state, country, and type of cancer or cancer gene. The website is: **http://cancernet.nci.nih.gov/wwwprot/genetic/genesrch.html.**

cancer cell. This understanding has allowed us to begin describing the evolution of specific cancers from predisposition to pre-cancer to cancer. Each cancer is ultimately defined by its particular pattern of altered and normal gene activity. This unique pattern determines the cancer's rate of growth, tendency to spread, responsiveness to hormones and therapies, and also predicts the ability of a person's immune system to recognize and respond to the cancer. Moreover, cataloging these molecular patterns will ultimately tell us how many different cancers exist and enable us to distinguish each cancer from its normal counterpart. Advances in our ability to detect, diagnose, and treat each cancer will most likely be found in these differences.

Cancer Risk

Cancer risk is the probability that the disease will occur in a given population. Research on cancer risk seeks to identify populations with a significant probability of developing cancer. By identifying populations with different probabilities of developing cancer, researchers can identify and quantify risk factors. Moreover, since cancer is a multistage process, risk factor analysis leads to the development of prevention and control strategies, early detection methods, and in some cases, more precise clinical intervention and management regimens.

Epidemiology is the principal discipline used to study cancer patterns, identify populations at risk, and establish cancer risk factors. Epidemiologists have uncovered distinct cancer patterns among various groups and continue to pinpoint previously unrecognized risk factors. For example, women in Asian countries have some of the lowest rates of breast cancer in the world, while women in the West have among the highest. But when Asian women migrate to the United States, their breast cancer risk rises over several generations until it matches that found in women in the United States. Upon further investigation, our scientists discovered that the increase in breast cancer risk was related predominantly to weight changes, particularly weight gain during the decade preceding breast cancer diagnosis. This finding incriminated certain aspects of American lifestyles such as dietary and exercise patterns. Moreover, it illuminated a major public health implication — that weight maintenance or reduction as an adult, accompanied by specific changes in diet and physical activity, may have a significant and rapid impact on breast cancer incidence. Studies such as these demonstrate NCI's commitment to address the burden of cancer in all population groups in the United States and ensure that all benefit from our research.

The epidemiologic approach has been successful in identifying many factors that increase cancer risk; most of these are related to environment and lifestyle, while others are part of a person's genetic makeup. With the exception of a few genetic conditions, however, it is still not possible to predict with any degree of certainty that a person having one or more of these factors will develop cancer. This uncertainty is related to the very nature of cancer, and the need for many specific alterations to accumulate in the DNA of a single cell for that normal cell to be transformed to a malignant state.

With recent major advances in molecular biology, a strategy known as molecular epidemiology has emerged. Molecular epidemiology enables us to combine biological markers (i.e., measurements of carcinogenic exposure, biologic response, and individual susceptibility) with traditional epidemiologic methods. Recent molecular research has provided evidence that environmental factors contribute to human cancers and that their risks are strongly influenced by inherited and acquired genetic susceptibility.

As this research continues, it remains true that the single most important exposure that increases cancer risk is the use of tobacco products, particularly cigarette smoking. Smoking is believed to

contribute to more than 30 percent of all cancer deaths. In addition, certain aspects of the diet, particularly diets lacking in fruits and vegetables or high in certain fats, seem to be important contributors to cancer risk. Greater than average cancer risk also has been linked to alcohol consumption; exposure to radiation (for example, ultraviolet and x-rays), certain occupational agents such as asbestos, and environmental pollution (for example, arsenic); consumption of some pharmaceutical agents (for example, estrogenic drugs); infection with viruses such as the human immunodeficiency virus (HIV) or the human papillomavirus (HPV); and hormonal factors.

Cancer Interventions

Ultimately, the purpose of understanding tumor biology and cancer risk is to discover more effective ways of preventing, detecting, diagnosing, and treating cancer. Although the full realization of this process lies ahead, important advances achieved over the past quarter century give ample reason for optimism.

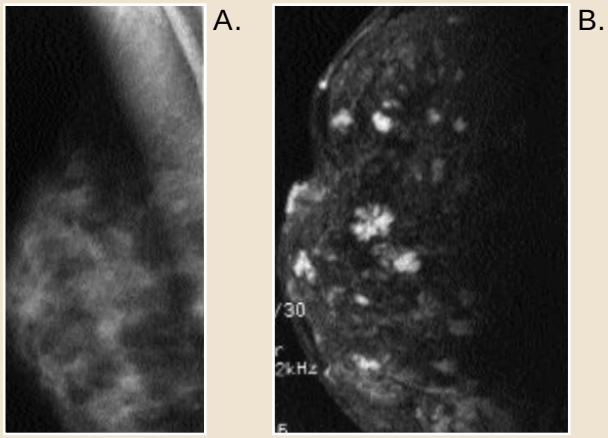
Our ability to prevent cancer depends on identifying, removing, and/or reversing the effects of specific risk factors. Approximately 90 percent of the skin cancers expected to occur this year could have been avoided through the use of protective measures against sunlight. Avoidance of smoking and use of other tobacco products could reduce the incidence of lung cancer by 80 percent and significantly reduce the rate of other cancers, including cancers of the pancreas, kidney, and head and neck. The adoption of diets containing less fat and more fruits and vegetables could diminish the incidence of some cancers, and physical activity may be associated with a lesser risk of several common forms of cancer, most notably colon and breast cancers.

NCI conducts and supports research into behavioral aspects of cancer prevention, such as smoking cessation and dietary interventions, including trials of dietary modification to reduce cancer incidence, dietary fat reduction to reduce recurrence of breast cancer, and high-fiber, low-fat, high fruit and vegetable diets to reduce recurrence of large intestine polyps. The Institute also supports research into chemoprevention, including the ongoing clinical trials of tamoxifen to prevent breast cancer, finasteride as a prostate cancer preventive, and aspirin to prevent recurrence of colorectal cancer. In 1997, a new Division of Cancer Prevention was established to coordinate NCI's prevention research. The new division will bring added visibility, prominence, and strength to the prevention research that NCI sponsors. In addition, an in-depth review of NCI's prevention program was completed in summer 1997. The review group's recommendations will be a guide for strengthening cancer prevention research.

At the Cutting Edge

Breast Imaging Technologies

X-ray technology saves lives. It is not, however, a perfect test for finding early breast cancer, particularly among younger women, in whom the density of normal breast tissue often makes the detection of very small cancers difficult. One approach to better breast cancer detection may be MRI. Panel A shows the x-ray mammogram of a 35-year-old woman with a strong family history of breast cancer and a normal breast physical exam; there is no evidence of cancer. In panel B, a magnetic resonance image from the same breast shows white areas. Tissue examination later confirmed that these were areas of cancer. The NCI is supporting a large multicenter study that will define the diagnostic value of MRI in women with abnormal mammograms.



Photos courtesy of Dr. Mitchell Schnall, University of Pennsylvania

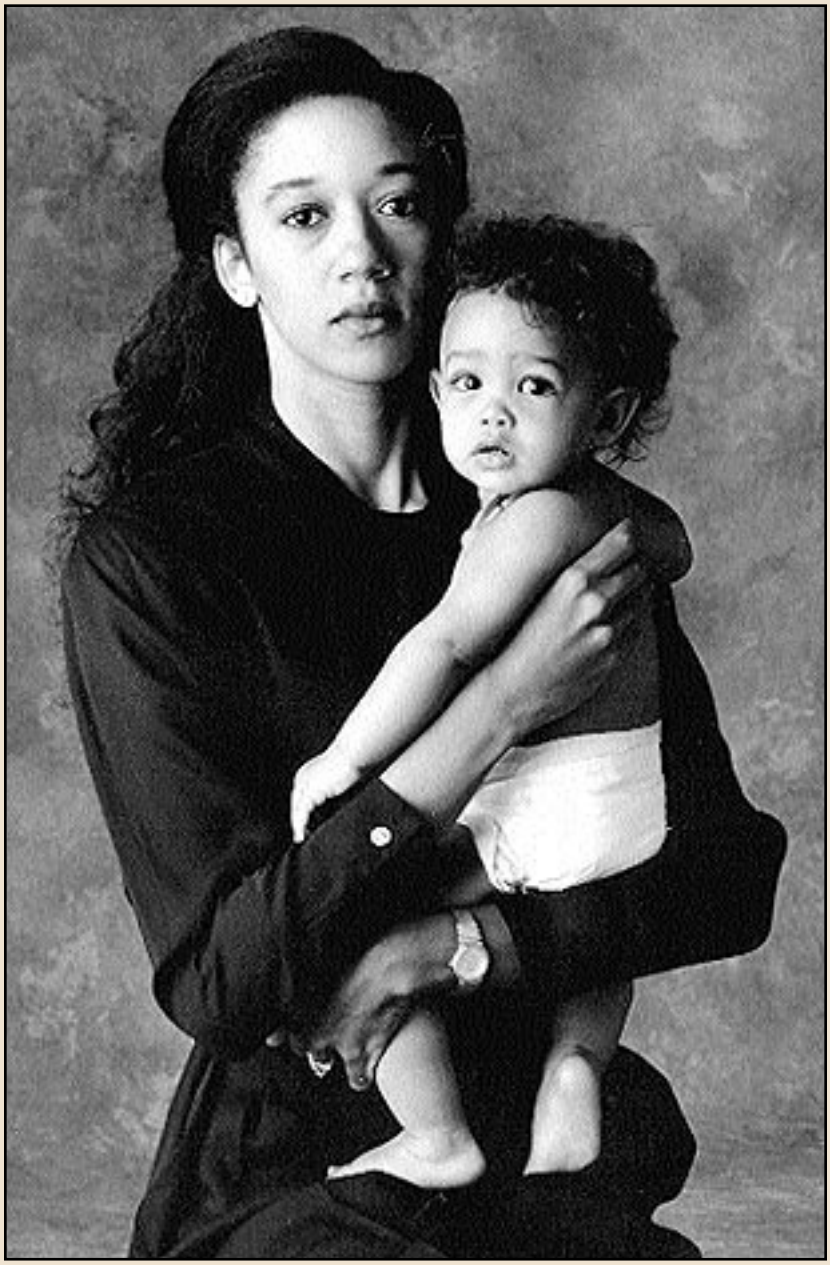
We have learned to see inside the bodies of living human beings and detect tumors with a precision that could not have been anticipated by a previous generation of physicians. Computed tomography, magnetic resonance imaging, and ultrasonography simply did not exist as useful clinical tools just over 25 years ago. Today, these technologies enable us to locate internal tumors with unprecedented accuracy, and to biopsy internal organs without the need for major surgery. There is every reason to believe that continued improvement in their powers of resolution will enable us to detect small tumors even earlier than is possible with currently available methods, such as x-ray mammography. Invasive detection and diagnostic procedures such as colonoscopy and bronchoscopy are gradually giving way to "virtual" procedures that use data from MRIs, CT scans, and x-rays to generate a 3-D computerized image of an internal structure without invading the body with scopes.

Currently, the diagnosis of cancer depends principally on the microscopic appearance of tissue samples taken from growths or other suspicious lesions in the body. Advances in biological knowledge, however, have improved our ability to subclassify cancers into accurate categories. Classifying cancers more precisely is important because it will enable us to better predict patients' clinical outcome and refine therapies. For example, our expanded understanding of normal immune system development and biology has led directly to molecular techniques for classifying immune system tumors (lymphomas). This experience with lymphoma is a model for what will very likely occur in a variety of malignancies, including neuroblastoma, a rare childhood cancer, which we now know has at least two forms — one that sometimes regresses and may need little treatment and one that advances rapidly and requires aggressive treatment. We expect that tumor diagnosis and classification will be revolutionized in the coming years as we apply emerging knowledge in molecular genetics. Some of this information will be gained through NCI's newly established Tumor Gene Index, which will catalog the genetic characteristics of tumors at each stage of growth.

The past quarter century has seen major progress in our ability to treat certain cancers. In addition to well-publicized improvements in the cure rates for many uncommon types of cancer, such as Hodgkin's disease, certain lymphomas, testicular cancer, and a variety of childhood cancers, combining chemotherapy with surgery and/or radiation has increased survival rates for patients with breast, colorectal, and non-small cell lung cancers. High-dose chemotherapy with stem cell rescue is effective treatment for leukemias and is undergoing definitive testing in breast and ovarian cancers. The application of molecular biology to the drug discovery process has ushered in the era of biological therapy by permitting the large-scale production of so-called "recombinant" proteins; as a result, the availability of interferon alpha-2b has markedly improved the outlook for patients with a rare form of leukemia. Both interferon and interleukin-2 provide improved symptom control for some patients with kidney cancer. Bone-marrow stimulating agents have improved supportive care by reducing the toxicity of chemotherapy to the blood elements. Over the past 15 years, the formidable problem of treatment-related vomiting has been lessened dramatically by the development of truly effective new drugs.

NCI is committed to research to improve the quality of life for those who develop cancer. As treatment becomes increasingly effective, the population of cancer survivors will continue to grow; we can also expect that problems associated with long-term survival will continue to emerge. Responding to these trends, NCI has established the Office of Cancer Survivorship to address the needs of cancer survivors and conduct research needed to answer important questions about quality of life and the development of secondary cancers. The first problem to be addressed is the challenge to an optimal quality of life posed by the effects of cancer treatment itself. Although most acute side effects of treatment are rapidly reversible, some, such as the loss of a limb, have a lasting impact. The widespread use of techniques such as breast reconstruction, conservative surgery, and customized limb prostheses have greatly improved the emotional and functional outlook for survivors of breast and bone cancers. The knowledge, gained in a landmark clinical trial, that chemotherapy followed by radiation treatment is as effective as total removal of the voice box for cancer of the larynx has made natural

Adult Survivors of Childhood Cancers



I was 12 when I was diagnosed with Hodgkin's disease — stage II. I was treated with radiation and chemotherapy, and my Hodgkin's was cured. Luckily for me, because I was treated on an NCI-sponsored clinical trial, I've been followed especially closely. I just turned 27, and at my last check-up, a small breast cancer was found.

Survivors of childhood and adolescent cancers, a growing population that by the year 2000 will number one in 900 adults, are at increased risk of second malignancies. For example, girls treated with radiation therapy to the chest for Hodgkin's disease have been found to be at significantly increased risk of breast cancer, usually about 10 years after diagnosis. Risk appears to be highest among those diagnosed in late childhood and those receiving higher dose radiotherapy. Adult survivors of childhood cancers may also be at greater risk of other solid tumors, leukemias, fertility loss, and other health problems, depending on the treatment they received.

My doctors knew I was at higher risk for breast cancer because of my radiation treatment, so they discussed with me the early warning signs for breast cancer and I started having mammograms when I was 25. That helped to catch this breast cancer so early.

Our expanding knowledge of long-term effects of cancer therapy is helping us tailor alternate therapies to minimize the risk of second cancers and other illnesses. For example, we now know that children with early stage Hodgkin's disease can be treated effectively with combination chemotherapy alone, or with low-dose radiation that reduces the risk of breast or other second tumors.

I'm happy to be alive, after two bouts with cancer, and I'm grateful to my doctors, and thankful for the excellent care I've received. But sometimes I get angry, and scared. Why did this happen to me? Will long-term effects of my treatment continue to affect me as I get older? And what if the cancer comes back?

Continuing improvements in cancer detection and treatment mean that more people than ever before are surviving cancer and living longer, fuller lives. To address the unique medical and psychosocial needs of this population, NCI has established a new Office of Cancer Survivorship to promote research on issues affecting survivors of all ages, and to accelerate the growth of knowledge about late effects of cancer treatment and the psychosocial concerns of survivors. A primary focus of this new office is to support research into enhancing the quality of life of cancer survivors throughout their lives.

speech preservation possible for many patients with this condition. FDA-approved drugs for protecting against the cardiac toxicity of the anthracycline antibiotics (used in the treatment of several types of cancer, including breast cancer and lymphoma) and the kidney toxicity of cisplatin (an important treatment for testicular and ovarian cancers) are expected to reduce the overall incidence of two particularly troublesome chronic effects of treatment.

The second problem to be addressed is the tendency of many cancer survivors to develop second cancers at the same or other body sites. In some cases, this too is a treatment effect, since many current therapies that effectively treat the patient's primary cancer unfortunately promote the development of second cancers in a small fraction of people who receive them. For example, certain chemotherapy regimens are associated with late appearing acute leukemia in some patients, often many years after treatment. Sometimes, however, second cancers are unrelated to cancer therapy. Patients who survive a first cancer of the lung or oral cavity, for instance, have a high incidence of subsequent tumors at those sites, probably because of the continued carcinogenic influences of tobacco. Inherited risk may also play a role. Some breast, ovarian, and colorectal cancer patients have a genetic predisposition to those cancers and are likely to develop second primary cancers. The solution to these persistent problems is clearly to discover more targeted and less toxic treatments and to develop better surveillance and prevention strategies for people whose risk is elevated for reasons unrelated to treatment.

Psychosocial and behavioral research can make fundamental contributions to all aspects of cancer survivorship, improving the quality of life both for cancer patients and for those at increased risk of developing cancer. Psychosocial research investigates how cancer affects quality of life and finds ways to address survivors' needs so they can meet the everyday demands of life and regain their productivity. NCI is committed to such research to complement its cancer prevention, detection, and treatment research programs. We expect that this research will be of growing importance as genetic advances pose difficult prevention and treatment choices.

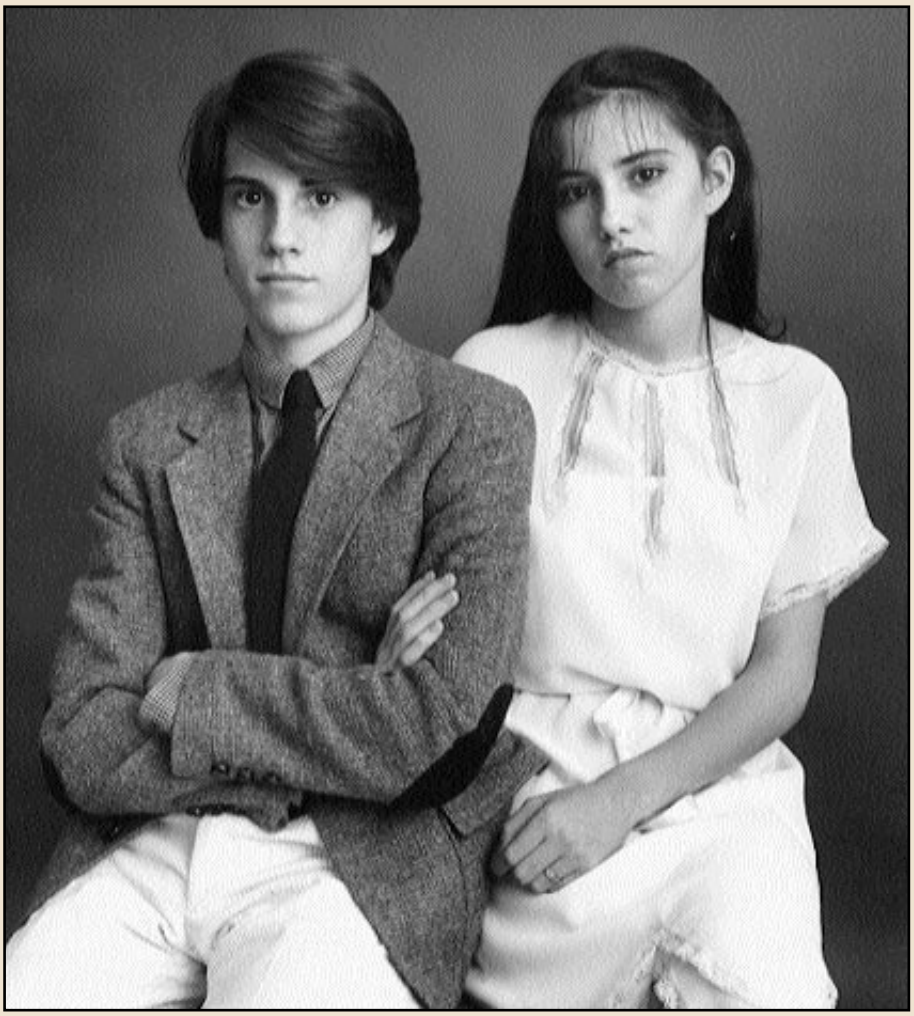
Pain control is one of the largest quality of life issues that face cancer patients as it can be one of the most debilitating side effects of the disease. NCI recognizes the need to expand its research into pain control methods and has several ongoing pain control-related clinical trials. In addition to these trials and currently available NCI patient publications on pain management, the Johns Hopkins University Oncology Center, through an NCI grant, has produced a patient/health professional resource, *Controlling Cancer Pain.* This resource includes a video and brochure, available in both English and Spanish, and a pain rating instrument. Johns Hopkins and NCI are now exploring a partnership for production of Web-based educational software to accompany the materials and distribution of the resource package. Finally, the Agency for Health Care Policy and Research has recently updated its guidelines for pain management for clinicians. A quick reference version for clinicians of *Clinical Practice Guideline: Management of Cancer Pain* can be found on the International Cancer Information Center's CancerNet™ Web site at http://cancernet.nci.nih.gov/clinpdq/supportive/Pain_Physician.html.

Cancer Control

Cancer control is the application of cancer research results and interventions to decrease the burden of cancer. Just as biology and epidemiology provide a foundation for intervention research, all three research areas provide a foundation for cancer control. The enormous challenges inherent in the effective application of research results are illustrated by the fact that despite decades of research, education, and outreach, more than one third of high school seniors — and over 20 percent of eighth graders — currently smoke.

The science of cancer control is necessarily multidisciplinary and involves behavioral research, epidemiology, health services research, and communications research. A cross-cutting theme is to identify the environmental, genetic, physiological, and psychosocial determinants of health in order to devise interventions that result in behavior changes that can reduce cancer risk and improve prognosis for people with cancer.

Children and Tobacco



All my friends smoke. It's no big deal. Anyway, I could quit if I felt like it. — 15-year-old-boy

The increasing use of tobacco by the Nation's children and teenagers is a national tragedy. Tobacco use is responsible for nearly one third of all cancer deaths in the United States, and responsible for nearly one in five deaths overall. But despite these sobering statistics, the use of cigarettes and other tobacco products among teenagers has risen every year since 1992. Over 60 percent of high school students have tried cigarette smoking, and about one third of high school seniors are current smokers.

Furthermore, tobacco use among teenagers is not limited to cigarettes: Smokeless tobacco use, which causes disfiguring and deadly oral cancers, is rising steadily, and a recent survey indicated that an estimated six million teenagers tried cigar smoking in the past year.

If current trends continue, more than five million of today's children will die prematurely from smoking-related illnesses. These deaths could result in almost $200 billion in future health care costs, and about 64 million years of life lost — the equivalent of about one quarter of the people in the U.S. each losing a year of life.

One of my friends quit smoking and she put on a lot of weight. I don't think I'll ever get lung cancer, but I definitely don't want to be fat. — 16-year-old girl

Preventing tobacco use among children and teenagers is a knotty problem. We know that if children do not begin smoking before their 20s, the chance of addiction is small. But we also know that peer pressure, media glamorization of smoking, and the seductive marketing strategies employed by tobacco companies can influence teenagers at a time in their lives when they're at their most adventurous, impressionable, and rebellious.

The NCI is committed to addressing the problem of tobacco use among youth. A 10-year national demonstration project, the American Stop Smoking Intervention for Cancer Prevention (ASSIST), has made youth a major focus of its interventions. Through media and educational campaigns, as well as efforts to strengthen enforcement of local anti-tobacco laws targeted at youth, ASSIST will reach 91 million people — approximately one third of the U.S. population, stop two million youths from becoming addicted to tobacco products, and prevent nearly 1.2 million premature deaths.

In addition, NCI has partnered with the National Institute of Child Health and Development and the National Institute of Nursing Research to fund innovative research projects aimed at understanding and controlling youth tobacco use. This multi-year project is the largest NCI anti-tobacco initiative aimed specifically at youth.

I only smoke at parties, or sometimes when I'm feeling stressed out. No way am I addicted. — 14-year-old girl

Behavioral research is central to cancer control because a large proportion of cancer is caused by or linked to specific, identifiable behaviors. Through behavioral research, we can develop interventions that encourage individuals and health care professionals to adopt or promote healthy practices, such as smoking cessation, adopting a low-fat, high-fiber, balanced diet, and undergoing recommended cancer screening.

Recognizing the importance of behavioral research, the NCI sponsored a Working Group on Behavioral Issues in Cancer Prevention and Control to identify research priorities for the Institute. Target areas identified by the Working Group include preventing tobacco use by children and teenagers, enhancing cancer risk communication and comprehension, integrating prevention and early detection services into health delivery systems, and improving accuracy and counseling related to genetic testing for cancer susceptibility.

Another important aspect of cancer control research is identifying the economic, social, and cultural factors that facilitate or discourage adoption of recommended screening regimens. For example, more than one half of women over age 50 do not get regular screening mammograms for breast cancer, despite clear scientific evidence that such screening saves lives. Since 1993, NCI has used a unique geodemographic database to identify the geographic locations and racial, social, and economic groups in which mammography rates are lowest. NCI uses this information to develop media and interpersonal outreach strategies targeted specifically to those groups.

Cancer control research often begins by studying cancer patterns in populations through epidemiological studies or through NCI's cancer surveillance system that monitors cancer incidence, mortality, and survival. Evaluating cancer patterns provides insight into who is developing cancer and what factors may have contributed to their disease. Researchers examine not only the changing burden of cancer, but also the knowledge, attitudes, and practices of the public and health professions related to cancer prevention, early detection, treatment, and rehabilitation. All of this information is essential for designing and evaluating interventions that may reduce the cancer burden. For example, surveillance data show that the incidence of non-Hodgkin's lymphoma (NHL) has risen steadily over several decades. Some of the recent rise can be attributed to the spread of AIDS, but most of the increase is occurring in the general population. This suggests the possible influence of an environmental agent, and ongoing research at NCI has suggested several factors that may be contributing to this increase: environmental exposure to herbicides and other pesticides, exposure to organochlorines, and nitrates in drinking water. NCI will soon begin a large-scale study to examine the role of these and other agents in the etiology of NHL.

Effective and widespread communication plays a critical part in applying the knowledge gained in biology, epidemiology, and intervention research. The NCI supports research on cancer communication and innovative programs to provide information on cancer to the public and to the Nation's health care providers. The NCI's communication systems provide Americans — patients, the public, and health professionals — with current and comprehensive information on cancer treatments and on effective prevention, early detection, and supportive care technologies.

New challenges for cancer control research abound. Our evolving health care system poses the dual challenges of introducing cancer discoveries in rapidly changing health care delivery settings, and of finding ways that clinical cancer research can be integrated into health care coverage, regardless of payer. Developing cost-effective cancer interventions is an essential part of cancer-related health services research. Discoveries in genetics and clinical science pose special challenges for cancer control. For example, more precise and individualized methods of assessing a person's risk of developing cancer have raised an array of new issues in living with and understanding risk. Cancer control research will be needed to help tailor prevention, detection, and treatment to individual needs.

Cancer Control is the final step in carrying out the basic mission of the NCI: To understand the nature of cancer and to apply that knowledge to reduce the cancer burden — the deaths and disabilities — so that all Americans can lead healthier and longer lives.

The National Investment in Cancer Research

The NCI conducts a wide-ranging, multi-faceted program of scientific research and other initiatives. The cornerstone of NCI's research program is investigator-initiated research — research that is proposed and conducted by scientists in laboratories, clinics and communities around the country. Over one half of the Institute's budget is devoted to such research, which is funded under a variety of peer reviewed grant mechanisms. These different mechanisms focus on single projects undertaken by individual investigators; on Program Projects that enable a team of investigators to develop a group of related projects; on awards for new investigators to enable them to develop a firm foothold in science; and on small business and industry-academic collaborations.

Peer review is fundamental to investigator initiated research. A grant application submitted to the NCI is reviewed by one of more than 100 committees, known as study sections or peer review groups, which are composed of scientists in fields closely related to the applicant's research. The reviewers give each grant a score reflecting the importance of the topic proposed, the rigor of the study design, and the investigator's ability to achieve the aims of the research. With the assistance of its principal advisory body, the National Cancer Advisory Board, the NCI examines each application and weighs the evaluation of the peer review groups, then critically assesses cancer research priorities and its budget in order to make funding decisions.

Unfortunately, worthy scientific ideas far outpace our ability to fund them — only about 25 percent of grants judged eligible for funding by the peer review groups actually receive funding. These difficult funding decisions must, therefore, be guided by overarching concerns.

Advocacy, in its broadest sense, is simply energetic support — support of a group, a cause, or an activity. NCI acts as a supporter/advocate for its many diverse constituencies by listening to those groups, understanding their needs, and acting on their advice.

To help us respond to the needs of the cancer community and forge productive partnerships with key groups, NCI has established several new offices:

Office of Special Populations Research (OSPR). The economically disadvantaged, the elderly, certain racial and ethnic minority groups — it is well known — that cancer burdens these groups in disproportionate measure. The OSPR was formed to provide a focus for these special problems. OSPR staff advise and assist the NCI Director and provide leadership and coordination on research related to minorities and special populations. They work with other NCI staff to define the scientific questions that NCI needs to address concerning cancer and special populations. In addition, the office researches the effectiveness of outreach activities aimed at specific groups.

Office of Liaison Activities. Throughout the Nation, hundreds of cancer advocacy and outreach organizations provide education and support to their communities. The Office of Liaison Activities is NCI's link to the national advocacy organizations and, through them, to the community-based groups. This office maintains ongoing communications and information exchange between the national cancer advocacy organizations and NCI, and cooperates and collaborates with these groups in areas of mutual interest.

Office of Cancer Survivorship. It is estimated that more than eight million Americans alive today have had cancer, over two-thirds of them diagnosed five or more years ago. The Office of Cancer Survivorship addresses the unique physical, social, psychological, and economic issues faced by these individuals. In consultation with the medical and consumer communities, this office develops, coordinates, and promotes research that will result in a better quality of life for this rapidly growing group.

Research on cancer involves activities from the most fundamental laboratory research to large-scale trials of cancer prevention and treatment methods. The NCI's cancer research funding strategy is to enable scientists to pursue the research areas with the *greatest scientific opportunity* — that is, the greatest opportunity to increase our knowledge of cancer. Funding decisions are based principally on the advice of scientists themselves as to those areas and projects that have the greatest potential to advance our knowledge of cancer. The ways in which a particular project can expand our understanding of cancer may not be immediately apparent. For example, NCI-supported scientists recently identified the gene for Gorlin syndrome, an inherited disease predisposing individuals to basal cell carcinoma of the skin and to congenital skeletal defects. A wholly unexpected finding was that the gene, known as *PTC*, is the human version of *patched*, a gene that has been studied at length in the fruit fly and the mouse. The discovery of *PTC*, coupled with our already extensive knowledge of *patched*, has paved the way for additional studies of basal cell carcinoma pathology and for the design of new therapies targeted to the specific defects brought about by *PTC* gene mutation.

A second critical factor that guides funding priorities, in addition to scientific opportunity, is the burden of specific cancers. For example, breast cancer, of which there are more than 180,000 new cases each year, is a major priority for NCI. Prostate cancer is the most prevalent cancer among men and, in fact, is the single cancer (excluding non-melanoma skin cancers) with the greatest number of new cases each year — approximately 209,900. Both of these cancers involve steroid hormone-dependent epithelial cells, and the tools and insights required to make progress against both are similar in many respects. Research on the hormonal aspects of testicular cancer, a relatively rare cancer with about 7,200 cases annually, may also provide clues to breast and prostate cancers. There is no research allocation schema that can account for these essential interrelationships between cancers. Understanding one type of cancer has the potential to advance our understanding of other cancers. For example,

The cancer research enterprise is vast, with many urgent and compelling needs and competing priorities. To ensure that it is wisely using its resources to meet the goals of the National Cancer Program, the NCI actively seeks out expert advice from a variety of advisory bodies from both within and outside the Institute. NCI's primary advisory groups include:

President's Cancer Panel. The President's Cancer Panel is responsible for monitoring and reporting annually to the President on the progress of the National Cancer Program and any barriers to its effective implementation in all populations.

National Cancer Advisory Board. NCI's principal advisory body is the Presidentially-appointed National Cancer Advisory Board. The board advises the NCI Director on issues related to the entire National Cancer Program and provides a second level of review for grant applications referred to NCI.

Boards of Scientific Counselors and Scientific Advisors. The Board of Scientific Counselors (BSC) reviews and advises Institute leadership on intramural research activities, whereas the Board of Scientific Advisors (BSA) makes recommendations for the extramural programs. Both the BSC and BSA are composed of outside scientists; in addition, the BSA includes members of the advocacy community.

Intramural Advisory Board & Extramural Advisory Board. The Intramural Advisory Board (IAB) and Extramural Advisory Board (EAB), composed of NCI intramural scientists and staff responsible for the review, award, and scientific management of the Institute's grant programs, meet regularly to advise the Institute on policy and process. Members also serve as information conduits for their staffs.

NCI Executive Committee. The NCI Executive Committee, which includes chairs of the IAB, EAB, BSC, and BSA, as well as division directors and other key advisors to the Director, meets weekly to make major policy and operating decisions for the Institute.

research on retinoblastoma, a rare eye cancer, has uncovered an alteration in the way a cancer cell communicates internally; this alteration is now believed to be found in all cancer cells. Studying this rare cancer, therefore, may yield clues to detecting common cancers earlier. Such advances may be made through targeted research, but more often spring from non-targeted fundamental, translational, or applied research.

Underlying the research conducted at and funded by NCI is an extensive set of mechanisms, organizations, and networks linking researchers, facilities, and information. This crucial infrastructure supports cancer research through diverse endeavors, including developing central resources in tissue and data banking; conducting directed programs in drug discovery and large scale screening for preventive agents; tracking changes in cancer incidence, mortality, and morbidity; and fostering the critically needed training of cancer researchers.

Like investigator-initiated research, most components of this infrastructure, including a network of Cancer Centers, Community Clinical Oncology Programs, and Clinical Trials Cooperative Groups, are funded through peer reviewed grants. Other components are funded under contract, such as the Surveillance, Epidemiology and End Results (SEER) Program, a network of cancer registries providing surveillance information on cancer incidence, mortality, and survival. The NCI's Frederick Cancer Research and Development Center is also funded under contract.

About the NCI Budget Estimate

This budget estimate outlines three vitally important levels of national investment in cancer research.

The first level of investment represents the Institute's Infrastructure for Discovery. This is the funding that is essential to enable current research to advance. It is sufficient to ensure stability, continuity, and progress in NCI's existing research programs in laboratory, clinical, and population studies aimed at the prevention, detection, diagnosis, and treatment of cancer and the rehabilitation of cancer patients. It is through these research

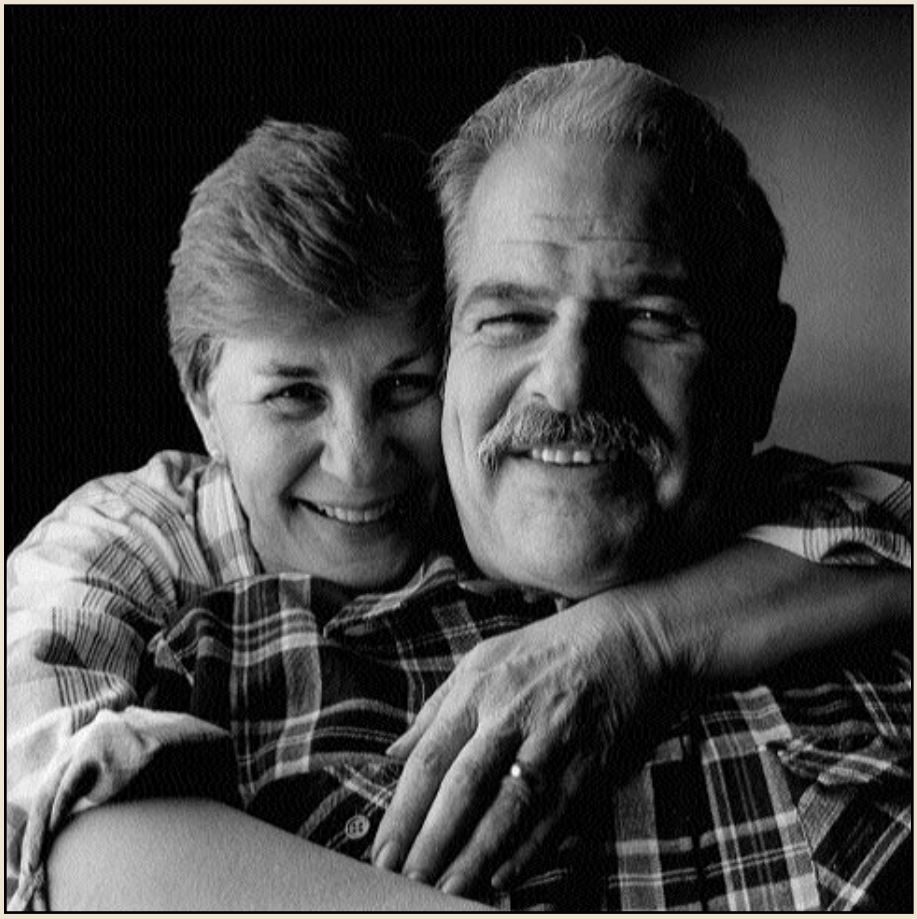
As NCI sets its research priorities, we turn to our extramural community, constituents, and advisory groups for their invaluable advice and suggestions. We do this through informal communications on a continuing basis. We also have set up several new types of planning groups to bring individuals together to focus on a particular area. Their recommendations and plans form the basis for far reaching transformations of the Institute's programs. Recent advice has resulted in the reorganization of prevention and control activities and the unification of extramural programs under one director. Drawing extensively on this expertise outside the Institute provides a rich source of ideas to ensure the best choices are made to fulfill our mission. It also provides the cancer community with a voice in the planning of our future directions and in important priority setting activities.

NCI Director's Working Groups. The NCI Director's Working Groups are ad hoc "think tanks" appointed to address key scientific issues such as cancer genetics, preclinical models of cancer, detection technologies, and developmental diagnostics. Their members include leaders in laboratory, clinical, and population-based research from the extramural and intramural research communities, staff of the NIH and other government agencies, members of professional organizations, and interested consumers and patient advocates. These groups' recommendations will provide input for strategic and operational planning.

Program Review Groups. Composed of outside experts, Program Review Groups provide in-depth reviews of broad organizational or trans-organizational programs. They focus on the effectiveness of a given program, solicit testimony from NCI staff and representatives of the scientific community, and provide recommendations for enhancing the structure and function of the program under study. They attempt to answer the key question of "What should the program be doing and how should it be organized to take advantage of present and future scientific needs and opportunities?"

Progress Review Groups. Progress Review Groups are composed of scientists, health professionals, industry representatives and lay advocates brought together to assess the state of our knowledge and identify scientific opportunity and need in such high-priority, cross-cutting areas of research as prostate cancer and breast cancer. NCI will use the Groups' recommendations to help set a national research agenda in these areas. Progress Review Groups in breast and prostate cancer were active during FY 1997 and will complete their work in FY 1998; a lung cancer Group will be under way by spring 1998.

Basal Cell Carcinoma



I've had basal cell cancers removed six times over the last 15 years. I know they are not as dangerous as other kinds of cancer, but still, there's the pain and scars from the surgery, and the cost. Time off from work, too. I also have to get checked every six months, and I can't help worrying that one of these things will go bad on me.

Each year, some 800,000 Americans are diagnosed with basal cell carcinoma (BCC) of the skin. Though rarely life-threatening, basal cell cancers can invade and destroy neighboring tissues, and can be disfiguring.

BCC can occur in a rare hereditary form known as Gorlin's syndrome, but it is most commonly non-hereditary (sporadic). Individuals with inherited disease are predisposed to skin cancer and may suffer congenital skeletal defects. The gene for Gorlin's syndrome, called *PTC*, was recently identified by NCI-supported scientists through studies of affected families, and also appears to be involved in some portion of sporadic BCC. An unexpected but exciting finding was that *PTC* is the human version of a gene known as *patched* that has been studied extensively in the fruit fly and the mouse. It has been shown to be important in the early stages of fruit fly development and for correct skeletal, limb, and neural development in the mouse. This extensive knowledge about the function of *patched,* developed in the laboratory by basic researchers, has provided crucial background information that dramatically accelerated study of the function of the human *PTC* gene.

According to NCI researchers, discovery of the *PTC* gene in humans paves the way for studies to learn about the biologic behavior of BCC and for designing new therapies that target changes brought about by *PTC* mutations. *PTC* appears to be involved in watching over the cell's cycle of growth and division — a tumor suppressor gene that, when working properly, shuts down tumor growth. It may be involved in or provide clues about other, more serious, epithelial tumors, such as breast and colon cancer. By studying *PTC* and other genes known to be mutated in BCC, we hope to identify why BCC does not spread, or metastasize, beyond the skin and apply this knowledge to preventing metastasis of other kinds of cancer.

My doctor says finding this gene that causes some basal cell cancers might lead to new treatments, like an ointment you could just put on your skin that would stop the cancer from growing. Now wouldn't that be great!

programs that we have achieved some of the most important recent advances in cancer, bringing us to a threshold of unprecedented opportunity.

The second level of investment enables the Nation to build rapidly on the enormous advances in knowledge and technology in certain areas through a significant expansion into crucial new areas of research. These distinct research areas cannot be pursued substantially under current fiscal constraints without damage to other vital research now under way. The proposed additional investment augments the core research program across the spectrum of inquiry in cancer biology, cancer risk, cancer intervention, and cancer control.

If we reduce current expenditures to pursue these new opportunities, we will undercut fundamental ongoing research, for example, on how cancer spreads from one organ to another, on the efficacy of a new prostate cancer treatment, or on the impact of diet on breast cancer risk. Limited aspects of each new investment area will be pursued under the maintenance budget, as projected here for FY 1999. But achieving the goals and reaching the milestones outlined in this document will require more resources than can be redirected from the core budget.

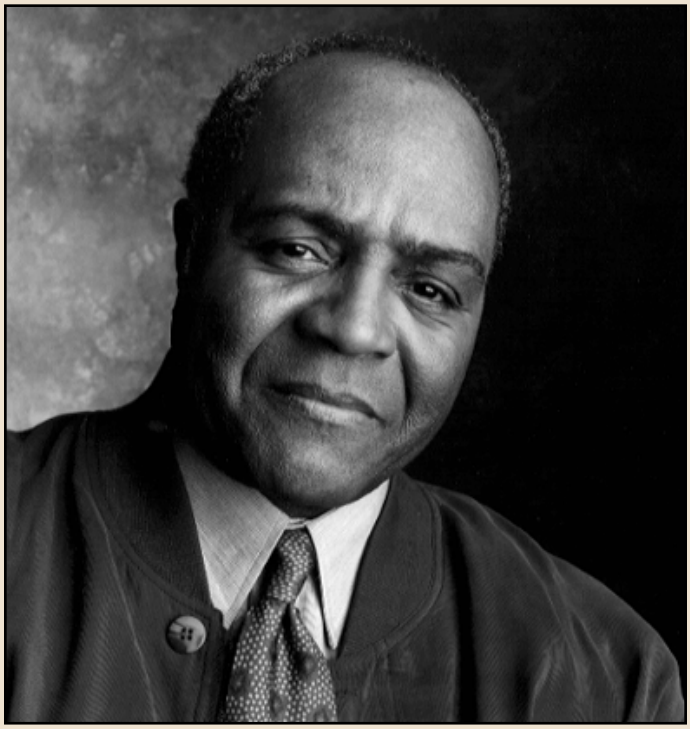
Finally, the third part of this document, "NCI's Challenge," describes NCI's vision of the steps we need to take to convert our knowledge of cancer, gained through our discovery process, into advances in cancer prevention, detection, diagnosis, and treatment. It is vital that we pursue these multiple strategies of research, maintaining a solid foundation and seizing opportunities when they present themselves. Only by doing so can we sustain a strong National Cancer Program.

NCI's Global Leadership

Because cancer knows no geographic boundaries, NCI maintains a comprehensive program of international activities, fostering information exchange and communication between American scientists and their colleagues around the world. NCI's international effort is coordinated by the Office of International Affairs (OIA). OIA acts as NCI's liaison with foreign and international agencies and coordinates cancer research activities under agreements between the U.S. and other countries.

NCI's recent activities in the international arena include a key role in the formation of the Middle East Cancer Consortium, an intergovernmental organization dedicated to increasing knowledge and decreasing the burden of cancer through cooperative efforts by countries in the region.

Prostate Cancer



There's a history of prostate cancer in my family, so I decided to get a PSA test after I turned 45. My doctor talked with me about the questions that surround PSA screening. I thought a lot about what she said and then, because of my family history, I decided to do it.

Prostate cancer is the most common cancer and the second leading cause of cancer death among U.S. men. In 1997, an estimated 209,900 new cases will be diagnosed, and 42,000 men will die of the disease. African American men have about a 37 percent higher incidence of prostate cancer than white men.

The PSA test for prostate cancer measures the level of prostate specific antigen (PSA) in a man's blood. It detects early stage tumors, and some have advocated the use of PSA for screening men 50 and older, and for men 45 and older with a family history of the disease. Yet it is still unknown whether or not screening saves lives, and some men may receive unnecessarily aggressive treatment for abnormalities found through screening. Because of these issues, most organizations of screening experts do not recommend it at this time and encourage men to understand the known risks and potential benefits of screening and aggressive treatment.

I'm not as worried about prostate cancer as I used to be. The treatments are improving, with fewer side effects and better chances for a cure.

Nerve-sparing surgery now reduces the risk of impotence or urinary incontinence, and for those who receive radiation treatment, computer imaging techniques help focus the radiation beam on the tumor, away from healthy tissue. Other advances include blocking hormones the prostate tumor needs to grow, destroying small tumors by freezing, and implanting tiny radioactive pellets directly into the prostate to deliver high dose radiation without exposing other parts of the body. All of these treatment options are currently being evaluated in NCI-sponsored trials.

The ongoing Prostate Cancer Prevention Trial (PCPT), a clinical trial involving 18,000 healthy men over age 55, will determine if the drug finasteride can prevent prostate cancer. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), a large NCI study, is assessing the efficacy of prostate cancer screening. Two trials, the Prostatectomy Intervention Versus Observation Trial (PIVOT) and Radiation Intervention Versus Observation Trial (RIVOT) are comparing patient outcomes with prostate removal surgery or radiation, respectively, and "watchful waiting" to distinguish patients needing aggressive therapy from those with slow growing tumors that will never threaten their lives.

My doctor also said scientists have just found the location of a gene they think may account for at least a third of prostate cancers in families where a lot of men are affected.

An NCI-supported international study of families with high incidence of prostate cancer has narrowed the location of the first hereditary prostate cancer gene *(HPC-1)* to chromosome 1. The gene itself has not yet been identified, but researchers estimate that about one in 500 men has an alteration in *HPC-1*. Familial prostate cancer accounts for about one in 10 cases, and *HPC-1* alterations are believed responsible for about a third of these.

To help ensure that men have accurate information about the options, benefits, and side effects associated with detecting, treating, and managing prostate cancer, the NCI has entered into a new national educational partnership with US TOO International, the largest men's cancer organization worldwide.

I'm hopeful that the new discoveries will mean that if I get prostate cancer we'll be able to make the best treatment decisions. Maybe by the time my sons are older, we'll know how to prevent prostate cancer altogether.

The NCI's Infrastructure for Discovery: Mechanisms and Requested Funding

Supporting the achievement of the goals and objectives of the NCI is an infrastructure of researchers, research institutions, training, and cancer surveillance. In this section we briefly outline the components of the infrastructure for discovery, the funding necessary to continue making advances against cancer, and examples of cutting-edge research the NCI supports. The budget figures for FY 1999 reflect a level of support sufficient to maintain the current discovery infrastructure, but insufficient to fund newly emerging areas of opportunity. New investment opportunities, along with the funding needed to support them, are outlined later in the document.

Research Project Grants

The "gold standard" of scientific accomplishment is the creation of new knowledge through research. The Nation's researchers represent the single most valuable resource of the research program. To foster the creativity of this vital national resource and provide the freedom to pursue the best ideas that will yield progress against cancer, NCI offers researchers throughout the country the opportunity to compete for research project grants.

The main pool of funds expended by the NCI on extramural research is known as the Research Project Grant (RPG) pool. These funds are competitively awarded through peer review to support individual cancer investigators in hundreds of academic, medical, public, and private research institutions located in almost every state across the country. Through 10 different types of individual awards, the NCI in FY 1998 anticipates expending more than $1.19 billion in support of over 3,700 separate research grants. Over 1,000 of these awards will be new or competing renewal projects.

Collectively, these research project awards span the full range of basic, clinical, and population-based studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, and control. These grant awards and the dedicated researchers behind them constitute the largest single categorical expenditure of resources that the NCI, through the extramural research community, commits annually to combat cancer. The scientific and medical advances that come from these invest-

At the Cutting Edge

Stopping Tumor Growth Dead in Its Tracks: Anti-angiogenesis Drugs

Just as a plant needs to be watered regularly in order to thrive, a tumor needs to be "fed" with fresh blood in order to grow. When the supply of nutrients is cut off, the tumor, like the plant, shrinks and dies. With this principle in mind, researchers are developing a new class of drugs to halt *angiogenesis,* the formation of new blood vessels that carry blood to the tumor.

There are several ways in which anti-angiogenesis drugs can work, such as stopping a cell's release of chemicals that send out the signal for new blood vessel development, or shutting down cellular communication at the vessel's construction site, making it impossible for the foundation for the new vessel to be laid.

Several anti-angiogenesis drugs have been shown to stop tumor growth in preclinical studies, and the drugs have had consistent and impressive anti-tumor activity in numerous animal tumor models. A first generation of these drugs, as well as related agents that block cells from invading a new area and metastasizing, are currently being tested in clinical trials. More potent compounds are being developed and should be entering clinical trials in the next one to two years.

RESEARCH PROJECT GRANTS (RPGS)

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Ongoing	$752,683	$829,722	$877,624	$909,023
*New	267,062	264,942	266,520	281,794
Subtotal	1,019,745	1,094,664	1,144,144	1,190,817
Small Business Innovation Research	35,643	45,952	47,399	49,058
TOTAL	**$1,055,388**	**$1,140,616**	**$1,191,543**	**$1,239,875**

*Includes both New and Renewal Awards

ments represent the irreplaceable intellectual capital upon which rests the future of cancer research and cancer care in this country and the world.

The Single Research Project Grant and Its Derivatives. The mainstay of the RPG pool is the single research project grant (designated R01) awarded to institutions on behalf of individual principal investigators. Recognizing the key role that individual investigators play in the cancer research enterprise, the NCI has, over the past year, shifted its funding priorities to increase significantly the number of new, investigator-initiated single project research grant applications that receive funding. This shift ensures that a greater number of promising research projects have the support they need to come to fruition. The single-investigator grant pay line rose from 15 percent to 23 percent in FY 1996, and we expect this pay line to be 23 percent in FY 1997. NCI has also instituted a second review process for unfunded grant applications whose merit rating falls near the pay line. More than 50 additional grants were funded through this new mechanism in FY 1996.

This support system has produced many of the most significant research advances in the NCI portfolio. For example, the discovery of *BRCA1*, the first confirmed hereditary gene for breast cancer, was announced by an NCI-supported grantee. The discovery of oncogenes that lead to cancer and their relationship to cellular genes, which earned the Nobel Prize for Physiology or Medicine in 1989, was made through this funding mechanism and continues to advance under NCI awards. Additionally, NCI has supported the discovery and development of important drugs such as paclitaxel (Taxol®) and tamoxifen, new methods of therapy including conservative surgery techniques for breast and prostate cancers, and adjuvant chemotherapy for all cancers.

The Program Project Mechanism. The Program Project Grant is an investigator-initiated multi-component award through which groups of researchers pursuing thematically related research projects that require additional shared resources, such as specialized core research facilities, can be peer reviewed and supported under a single award. The program project mechanism gives investigators access to a much broader range of projects and common access to patients and tissue samples that would be difficult, if not impossible, to arrange in a single project setting. This approach is especially useful in interdisciplinary and translational research in which basic and clinical projects are combined, fostering synergy between the investigators.

The value of this mechanism is exemplified by a large program project centered in Seattle that has led the way in developing both basic bone marrow transplant biology and its clinical application in high dose chemotherapy regimens for several types of cancer. In 1990, the Nobel Prize for Physiology or Medicine was awarded in conjunction with some of the work performed under this award.

Intramural Research

The NCI Intramural Research Program (IRP), which includes the Divisions of Basic Sciences, Clinical Sciences, and Epidemiology and Genetics, is dedicated to the comprehensive understanding of cancer. IRP scientists, technical and support staff, research fellows, and visiting scientists from around the world conduct basic, clinical, and population-based studies in all the areas of cancer research.

Many NCI intramural researchers are recognized leaders in their fields, as reflected by citations of their work by other scientists, their service on editorial boards of peer-reviewed scientific journals, and the prizes and honors they receive.

NCI intramural scientists collaborate with investigators in academia and in the biotechnology and pharmaceutical industries across the Nation and around the world to accelerate the application of new knowledge to development of products that will benefit human health.

The Institute takes great care to ensure careful stewardship of resources and uniform standards of excellence in a stimulating environment where young people receive mentorship, training, and inspiration and where scientists at all stages of their careers are encouraged to be creative and strive for critically important knowledge. These efforts are detailed in the widely distributed manual *National Cancer Institute: Intramural Organization and Principles.*

The IRP has long served as a training locus for cancer researchers in all fields, and many leading scientists across the country and in other nations have been trained in its clinics and laboratories. It continues to be an important resource for training the next generation of men and women who will continue the quest for knowledge that we will use to prevent, control, and cure cancer. In fact, three new granting mechanisms have been initiated in the IRP to further support training of new researchers, foster collaboration among NCI scientists, and promote the development and acquisition of advanced technologies. Depending upon the program, these grants will be awarded for from one to three years at a level of $60,000 to $65,000 per year and will enable intramural investigators to obtain funding for innovative and collaborative research or technology research and development beyond their usual budgetary allocation. The Division of Clinical Sciences' Intramural Research Award and Advanced Technology Awards programs have completed their first grant cycle, and the Division of Basic Sciences' Intramural Grants Award program will soon be under way.

The intramural clinical research program is housed principally in the NIH Warren G. Magnuson Clinical Center, where patients from across the country are treated on research protocols. The Clinical Center is a unique environment in which investigators throughout the NIH community develop and test novel therapies derived from our growing body of knowledge, facilitating the rapid transfer of new information from the laboratory to the patient and back to the laboratory.

INTRAMURAL RESEARCH

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Basic	$127,579	$130,377	$129,433	$136,158
Clinical	93,929	95,990	95,293	100,245
Epidemiology & Genetics	38,259	39,098	38,815	40,832
NIH Central Services	147,124	150,351	149,264	157,018
TOTAL	**$406,891**	**$415,816**	**$412,805**	**$434,253**

IMMEDIATE OPPORTUNITY

ADVANCED TECHNOLOGIES CONSORTIUM

Staying on the cutting edge through the use of technology is one of the greatest challenges facing any research institution. In response to this challenge, NCI has recently created an Advanced Technology Consortium that will help investigators in NCI's Intramural Program acquire, develop and implement innovative, state-of-the-art technology that is relevant to the prevention, diagnosis, staging, understanding, and treatment of cancer.

The Consortium will use various methods to accomplish its goals, including: organizing seminars for researchers and representatives from academic and commercial institutions to present their innovative technologies; acting as a liaison between investigators and outside organizations for the import, export, or refinement of a technology; and providing funds on a competitive basis for technology development and implementation.

By providing its Intramural Program scientists with an outlet to develop, refine, or acquire the tools necessary for them to succeed in their research efforts, NCI is clearly investing for success.

The IRP is central to the identity of the National Cancer Institute as a scientific organization. An important benefit for many physicians who manage NCI extramural grants and programs is the opportunity to spend part of each week doing research in the Clinical Center. Interaction between the scientists who manage the grant portfolios and the scientist-executives who direct the Institute and set its priorities enriches the quality of decision making and continually reminds us of our mission: to learn how to reduce death and suffering from cancer.

Cancer Centers

The NCI-supported Cancer Centers are 57 of the strongest institutions in the Nation dedicated to scientific innovation and excellence; to interdisciplinary research, training and education; and to the recognition and coordinated pursuit of new research opportunities. Cancer Centers are committed to using new knowledge, gained through research, to develop practical strategies that will reduce cancer incidence, morbidity, and mortality and to increase the survival and quality of life of cancer patients. These institutions have the dynamic, flexible research infrastructures and organizational capabilities that consistently promote and sustain the collaboration among basic, clinical, and population research scientists needed to address the complicated questions associated with cancer causation and progression. Research activities on the molecular and cellular dynamics of cancer cells, vaccine development, novel approaches to gene therapy, and prevention and control interventions all illustrate the need for such effective collaborative enterprises.

Cancer Centers achieve their objectives by providing a framework that stimulates the participation of researchers and clinics in highly diverse but complementary scientific areas. They provide ready access to the most advanced research technologies and services, assure a close association between state-of-the-art research and state-of-the-art care activities within the institution, develop key collaborations with industrial, community, and state health organizations, and link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions. With their broad geographic distribution, Cancer Centers are key partners and the NCI's principal vanguard in bringing research benefits directly to local communities and regions of the country.

During FY 1996, the NCI conducted an in-depth review of the Cancer Centers Program. The Program Review Group identified the program's strengths, as well as opportunities for improved performance, and made several major recommendations regarding the designation, structure, function, and review of Cancer Centers and the distribution and use of Cancer Center funds. The Program Review Group also proposed a greater role for Cancer Centers as key regional and national resources in the war against cancer.

CANCER CENTERS

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Clinical Comprehensive	$117,969	$118,761	$122,929	$133,327
Basic Research	19,325	19,635	20,206	21,566
Subtotal, Core Grants	137,294	138,396	143,135	154,893
SPOREs (P50)	25,374	28,402	28,000	29,280
Planning	723	381		
TOTAL	**$163,391**	**$167,179**	**$171,135**	**$184,173**

Clinical Trials

A strong clinical research structure, including a comprehensive program of clinical trials in treatment, early detection, and prevention, is a critical component of the NCI research program. The components of the program include the Cancer Centers described above and the Cooperative Groups described in the following section. The Community Clinical Oncology Program (CCOP) is also a crucial component, extending the opportunity for participation in clinical trials to communities across the country. Hundreds of clinical trials are supported through these and other

The National Cancer Institute Cancer Centers Program

■ Comprehensive Center Center ◆ Clinical Cancer Center ● Cancer Center

ALABAMA
■ *University of Alabama at Birmingham Comprehensive Cancer Center*
Birmingham, AL

ARIZONA
■ *Arizona Cancer Center*
University of Arizona
Tucson, AZ

CALIFORNIA
◆ *Beckman Research Institute, City of Hope*
Duarte, CA
■ *University of California at Irvine Cancer Center*
Orange, CA
◆ *University of California at San Diego Cancer Center*
LaJolla, CA
● *The Burnham Institute*
LaJolla, CA
● *Salk Institute Cancer Research Center*
LaJolla, CA
■ *Jonsson Comprehensive Cancer Center*
University of California at Los Angeles
Los Angeles, CA
■ *Norris Comprehensive Cancer Center*
University of Southern California
Los Angeles, CA

COLORADO
■ *University of Colorado Cancer Center*
Denver, CO

CONNECTICUT
■ *Yale University Comprehensive Cancer Center*
New Haven, CT

DISTRICT OF COLUMBIA
■ *Lombardi Cancer Research Center*
Georgetown University Medical Center
Washington, DC

HAWAII
◆ *Cancer Research Center of Hawaii*
University of Hawaii at Manoa
Honolulu, HI

ILLINOIS
■ *Robert H. Lurie Cancer Center*
Northwestern University
Chicago, IL
◆ *University of Chicago Cancer Research Center*
Chicago, IL

INDIANA
● *Purdue University Cancer Center*
West Lafayette, IN

MAINE
● *The Jackson Laboratory*
Bar Harbor, ME

MARYLAND
■ *The Johns Hopkins Oncology Center*
The Johns Hopkins University
Baltimore, MD

MASSACHUSETTS
■ *Dana-Farber Cancer Institute*
Boston, MA
● *Center for Cancer Research*
Massachusetts Institute of Technology
Cambridge, MA

MICHIGAN
■ *Barbara Ann Karmanos Cancer Institute*
Wayne State University
Detroit, MI
■ *University of Michigan Comprehensive Cancer Center*
Ann Arbor, MI

MINNESOTA
◆ *Mayo Cancer Center*
Mayo Foundation
Rochester, MN

NEBRASKA
● *Eppley Cancer Center*
University of Nebraska Medical Center
Omaha, NE

NEW HAMPSHIRE
■ *Norris Cotton Cancer Center*
Dartmouth-Hitchcock Medical Center
Lebanon, NH

NEW JERSEY
◆ *The Cancer Institute of New Jersey*
Robert Wood Johnson Medical School
New Brunswick, NJ

NEW YORK
■ *Memorial Sloan-Kettering Cancer Center*
New York, NY
■ *Roswell Park Cancer Institute*
Buffalo, NY
■ *Kaplan Cancer Center*
New York University Medical Center
New York, NY
■ *Herbert Irving Comprehensive Cancer Center*
Columbia University College of Physicians and Surgeons
New York, NY
■ *Cancer Research Center*
Albert Einstein College of Medicine
Bronx, NY
◆ *University of Rochester Cancer Center*
Rochester, NY
● *Cold Spring Harbor Laboratory*
Cold Spring Harbor, NY
● *American Health Foundation*
New York, NY

NORTH CAROLINA
■ *Duke Comprehensive Cancer Center*
Duke University Medical Center
Durham, NC
■ *Lineberger Comprehensive Cancer Center*
University of North Carolina School of Medicine
Chapel Hill, NC
■ *Wake Forest University Comprehensive Cancer Center*
Winston-Salem, NC

OHIO
■ *Ohio State University Comprehensive Cancer Center*
Columbus, OH
◆ *University Hospitals Ireland Cancer Center*
Case Western Reserve University
Cleveland, OH

OREGON
◆ *Oregon Cancer Center*
Oregon Health Sciences University
Portland, OR

PENNSYLVANIA
■ *Fox Chase Cancer Center*
Philadelphia, PA
■ *University of Pennsylvania Cancer Center*
Philadelphia, PA
■ *University of Pittsburgh Cancer Institute*
Pittsburgh, PA
◆ *Kimmel Cancer Center*
Thomas Jefferson University
Philadelphia, PA
● *Wistar Institute Cancer Center*
Philadelphia, PA

TENNESSEE
◆ *St. Jude Children's Research Hospital*
Memphis, TN
● *Drew-Meharry-Morehouse Consortium Cancer Center*
Nashville, TN
◆ *Vanderbilt Cancer Center*
Vanderbilt University
Nashville, TN

TEXAS
■ *The University of Texas M.D. Anderson Cancer Center*
University of Texas
Houston, TX
■ *San Antonio Cancer Institute*
San Antonio, TX

UTAH
◆ *Huntsman Cancer Institute*
University of Utah
Salt Lake City, UT

VERMONT
■ *Vermont Cancer Center*
University of Vermont
Burlington, VT

VIRGINIA
◆ *Massey Cancer Center*
Virginia Commonwealth University
Richmond, VA
◆ *University of Virginia Health Sciences Center*
Charlottesville, VA

WASHINGTON
■ *Fred Hutchinson Cancer Research Center*
Seattle, WA

WISCONSIN
■ *University of Wisconsin Comprehensive Cancer Center*
Madison, WI
● *McArdle Laboratory for Cancer Research*
University of Wisconsin
Madison, WI

The Special Role of SPOREs

Specialized Programs of Research Excellence (SPOREs) are programs that focus on translational research (research designed to move laboratory discoveries into patient and population research settings). Cancer centers are eligible to obtain support through the SPORE program, although other research institutions are also eligible to compete for SPORE awards. Every year, SPOREs around the country produce important scientific findings and conduct groundbreaking translational research. For example:

The breast and ovarian cancer susceptibility gene *BRCA2* was identified by researchers at the Breast Cancer SPORE at the Duke University Comprehensive Cancer Center. Other studies have indicated that specific mutations in *BRCA2* or in *BRCA1*, the first identified "breast cancer gene," are present in as many as one in 40 Ashkenazi Jewish women (Jewish women of Eastern European descent). While researchers at other institutions are beginning to understand more precisely the risk of breast and ovarian cancers conferred by mutations in *BRCA1* and *BRCA2,* the Duke team is continuing its study of both genes at the molecular level. Equal attention is being paid to practical issues of testing for these genes and helping women to make informed decisions about testing.

Large numbers of women diagnosed with ductal carcinoma *in situ* (DCIS) are treated by mastectomy, although it is not known how many of these very small tumors will eventually develop into invasive cancer. The University of California, San Francisco (UCSF) Breast Cancer SPORE is collaborating with other SPOREs to establish a DCIS registry and tumor tissue and nucleic acid banks to facilitate research on the prognosis and treatment of DCIS. The work on DCIS at UCSF has expanded into a consortium involving all six Breast Cancer SPOREs — a networking effort that exemplifies the kind of activity at which SPOREs excel.

research mechanisms, such as individual research grants, program project grants, cooperative agreements, and contracts.

Our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. In the past, institutions have used surplus revenues from patient care services to supplement government research support. The growth of managed care has all but eliminated those discretionary funds. As a result, institutions can no longer sponsor research activities requiring capital expenditures and cannot support essential training for young investigators. These changes pose a very real danger for the continuation of cancer research and our continued progress against cancer.

To combat these undesirable effects of changes in the health care system, we have begun looking for ways to increase access to clinical trials. For example, an innovative 1996 agreement between NCI and the Department of Defense (DoD) has given thousands of DoD cancer patients more options for care and greater access to state-of-the-art treatments. Under the agreement, patients who are beneficiaries of TRICARE/CHAMPUS, the DoD's health program, are allowed to participate in NCI-sponsored Phase II and Phase III clinical treatment trials. In the past, DoD coverage was limited for medical care delivered as part of a clinical trial. NCI and DoD are refining a system that allows physicians and patients to determine quickly what current trials meet their needs and where they are taking place. By increasing enrollment in clinical trials, this partnership will benefit patients and will help us answer more quickly key scientific questions about cancer.

Clinical Trials Infrastructure

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
TREATMENT:				
Clinical Cooperative Groups	$89,244	$88,462	$92,960	$101,214
Community Clinical Oncology Program	20,500	25,150	25,468	26,629
PREVENTION:				
Community Clinical Oncology Program	17,463	21,424	21,695	22,684
TOTAL	**$127,207**	**$135,036**	**$140,123**	**$150,527**

An even wider-ranging agreement with the Veterans Administration, which provides medical care to about 2.9 million veterans each year, will allow eligible veterans of the armed services to participate in NCI-sponsored prevention, diagnosis, and treatment studies.

Cooperative Group Clinical Trials Program. The nationwide Cooperative Group program promotes and supports clinical trials in cancer treatment, prevention, and early detection. More than 1,400 institutions and 8,500 investigators participate in these Cooperative Group studies.

The sheer number of different types of cancers and the biological complexity of individual cancers present extraordinary challenges to the efficient clinical investigation of new anti-cancer agents or new treatment strategies suggested by laboratory and animal experiments. To more rapidly test potential treatment advances in patients, the NCI maintains a standing funded clinical trials program to conduct such investigations. In this way, new clinical trial organizations do not have to be created each time a potential new cancer treatment emerges. Nine NCI-sponsored Cooperative Groups place approximately 20,000 new patients onto cancer treatment protocols annually, principally large randomized Phase III clinical trials that have been responsible for establishing the current state of the art for cancer treatment worldwide.

In addition, new anti-cancer agents being studied for the first time in patients are tested through Phase I and Phase II clinical trials; many of these early treatment clinical trials are conducted under NCI Investigational New Drug (IND) sponsorship in institutions funded by NCI cooperative agreement grants. Close to 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are being studied under NCI INDs. Many of these agents are being developed clinically as a result of active NCI cooperation with biotechnology and pharmaceutical companies, accelerating the clinical testing of scientific advances emerging from these sources. Others come from the scientific laboratories and discovery programs of the NCI itself. Examples of important

New Approaches to Therapy

When we think of cancer treatment, we think of surgery, radiation, and chemotherapy — the traditional mainstays of treatment. NCI is committed to improving these standard treatments through research and is developing new agents which enhance the effectiveness of these approaches by making the cells more sensitive to the treatment. In addition, the NCI is exploring novel treatment approaches including inhibition of cellular signals which activate tumor growth and stimulation of the body's own immune system to destroy tumors.

Signal Transduction Inhibitors: Scientists are now developing drugs that target the genes that enable cancer cells to proliferate. One such drug, Flavopiridol, halts the activity of an enzyme required for cells to divide. After extensive preclinical testing at NCI, it has recently been used to treat cancer patients with promising early results. Flavopiridol may also be useful in improving the effectiveness of conventional chemotherapy.

Cancer Vaccines: The hope of eliminating growing cancers in patients might be realized through cancer vaccines made from tumor cells. After a patient receives vaccine, it is hoped that their immune system will react by attacking the tumor cells introduced by the vaccine, and in so doing begin to eliminate tumor cells already in the body. Vaccines have been made substantially more potent by an improved understanding of how the body's immune system gears up for action. Vaccines made from tumor cells are now being tested for patients with melanoma, colon cancer, breast cancer, prostate cancer, and lymphomas.

Multi-Modality Treatment: Using combinations of treatments and drugs to combat cancer is not a new idea, but now advances are likely with the addition of agents that can improve the effectiveness of radiation. Gadolinium Texaphyrin appears to sensitize cells to the killing effects of both radiation and chemotherapy. It is absorbed by tumors to a much greater extent than by healthy tissue and, therefore, makes the tumor more susceptible to killing. Use of this drug holds particular promise for the treatment of brain tumors. It will be used to augment both conventional external beam radiation and the newer technique of stereotactic radiotherapy, which uses three-dimensional imaging to precisely deliver radiation to a tumor.

Natural Products

Every day, teams of researchers around the globe venture forth to identify and collect plants and marine organisms that can be tested for their anti-cancer activity. These NCI-supported teams can be found in Madagascar, Southeast Asia, Africa, the coral reefs of the Indo-Pacific, or right here in the United States. In addition, samples are collected and sent to NCI through scientific collaborations that have been formed between NCI and organizations in countries such as Brazil, China, Costa Rica, New Zealand, and Zimbabwe.

Each year NCI's Natural Products Branch receives about 2,000 plants and 1,000 marine organisms for testing. From these samples, over 6,000 unique extracts are prepared and screened at the NCI's Frederick Cancer Research and Development Center for their ability to work against 60 human cancer cell lines. About 200 extracts per year show activity against three or more cell types, and these are examined in detail by NCI-supported intramural and extramural researchers.

Once a compound showing promise against cancer has been discovered, the specific cancer-fighting chemical must be identified and the long process of drug development begun. Development may be done at NCI, but sometimes takes place at a pharmaceutical company that has an agreement with NCI. Following initial development and preclinical trials, the drug is tested in people to determine its effectiveness. If the drug works well, it may be on its way to being approved by the Federal Food and Drug Administration and added to the growing arsenal of anti-cancer drugs.

However, natural products active against cancer are hard to find. Even if an extract demonstrates anti-cancer activity when tested in the lab, there is no guarantee that the drug will work well in cancer patients. Effective natural products discovered by NCI-supported researchers include paclitaxel, which comes from the bark or needles of a yew tree, and is used to treat breast and ovarian cancers. Another success is the ovarian cancer drug topotecan made from the compound camptothecin isolated from the bark of a Chinese tree. NCI also played a major role in the development of vincristine and vinblastine, both of which come from the rosy periwinkle and helped turn the tide against some lymphomas and childhood leukemias. Being tested in early clinical trials against a broad spectrum of cancers are bryostatin-1 and dolastatin-10, both of which come from marine organisms.

As you read this, the hunt for new cancer fighting natural products continues in the hope that other effective cancer therapies exist in the natural world.

anti-cancer agents that have come from NCI development include paclitaxel (Taxol®) for ovarian and breast cancers, interferon alpha-2b for malignant melanoma and chronic myelocytic leukemia, fludarabine for chronic lymphocytic leukemia, and all-trans retinoic acid for acute promyelocytic leukemia.

Science is increasingly delineating the distinct biological basis for many tumors. As a result, many clinical trials of new treatments are linked to particular laboratory studies, and many NCI trials now include laboratory components in addition to the clinical evaluations. For example, clinical studies of new acute leukemia treatments now routinely include the analysis of genetic changes in the malignant leukemia cells of the individual patient. The NCI has funded small clinical trials groups specifically to evaluate potential new treatments for patients with brain tumors, malignancies occurring in AIDS patients, and pediatric tumors, due to the very specialized nature of these cancers.

Participation of members of special population groups in clinical research is a high priority for the Institute. A recent NCI evaluation has shown that minority populations participate in treatment clinical trials in proportion to their cancer incidence; two new grant programs are supporting research on ways to increase participation of women and minority individuals in prevention and screening studies. Interventions are being tested on recruitment methods and steps to retain participants through the course of a trial.

Greater patient access to advanced therapeutic approaches has been a chief goal of the NCI clinical trials program. The field of childhood cancers is a success in this regard. About 95 percent of children up to age 14 who develop cancer are evaluated at a Cooperative Group institution; of these, 70 percent participate in one or more clinical trials. The number of children participating in clinical trials may increase with the establishment of the Pediatric Cancer Care Network. This network, a cooperative agreement between the Children's Cancer Group, the Pediatric Oncology Group, and the Blue Cross/Blue Shield System (BC/BS) nationwide, will ensure that children of BC/BS subscribers receive care at designated centers of cancer care excellence and will promote the enrollment of children in Cooperative Group clinical trials. While the percentage of adult cancer

Conservative Breast Cancer Therapy

My gynecologist called to say my mammogram showed a change from last year. She sent me to a surgeon for a biopsy. The results came back — breast cancer. I'm 50 years old, but the first thing I thought of was losing my breast. I was terrified at the prospect of being so disfigured, but they told me they could treat the cancer just as well without doing a mastectomy. I was so relieved, grateful — hopeful for the first time since my diagnosis.

Breast cancer is expected to strike over 180,000 American women in 1997; the lifetime risk of having the disease is one in eight. The total breast amputation suffered by past generations of women with breast cancer is no longer a necessary component of treatment for many women. Up to 15 years of patient follow-up in several randomized, controlled trials performed in the U.S. and abroad have shown that conservative therapy — defined as removal of only the tumor itself (lumpectomy) and the adjacent underarm lymph nodes, followed by radiation of the entire breast — results in survival equivalent to modified radical mastectomy. A surgical oncologist recounts:

Previously, surgeons concentrated on removing as much breast tissue as possible because it was believed that breast cancer spread by permeating the surrounding tissues. Mastectomy did decrease recurrences in the region of the breast, but survival was not improved because patients died of distant metastases. Better understanding of breast cancer biology resulted from research demonstrating that metastatic spread occurred principally via lymph and vascular channels. This finding led us to suspect that radical breast surgery was unnecessary.

The few remaining barriers to conservative therapy relate primarily to the size of the tumor relative to the breast size. With heightened patient and physician awareness and growing use of detection measures such as mammography, breast tumors are increasingly being discovered when they are small, well-defined, and amenable to conservative treatment. Over half of breast tumors discovered today are under two centimeters in diameter with no lymph node involvement. In addition, recent studies by the National Surgical Adjuvant Breast and Bowel Project show that using chemotherapy before surgery (neoadjuvant therapy) actually shrinks tumors, enabling a larger percentage of women to have conservative treatment. Ongoing clinical trials have focused on testing whether breast irradiation is essential after breast conserving surgery. An NCI radiation oncologist sums up the results:

Radiation of the breast is a critical part of the conservative approach. To date, we have not found any group of patients with invasive breast cancer that can safely have this therapy omitted. It is reasonable to continue to study this in carefully monitored clinical trials, but only in patients at low risk of local recurrence who are well informed and accept the risk of omitting radiation.

Our challenge now is to rid the body of micrometastases that occur in many patients before the tumor is removed surgically. Systemic chemotherapy and hormonal therapies designed to combat these distant metastases have improved patient survival in clinical trials. Researchers are working to develop more potent adjuvant systemic therapies for patients whose tumors are unlikely to be cured by local therapy alone. We believe the recently achieved drop in breast cancer deaths for women reflects in part the wider use of effective adjuvant systemic treatment in the community at large. As these therapies improve, the day may even come when surgery is no longer required.

My doctors gave me a choice — I chose breast conserving surgery because it left me whole and because it was the best choice for me and my family. The studies assured me that it was a safe thing to do. It has meant everything to have these options.

Special Populations Activities at the NCI

Cancer is a burden for everyone it touches, but it hits certain groups particularly hard. The elderly, the economically disadvantaged, and certain racial and ethnic minority groups are diagnosed with cancer more often — frequently at later stages of the disease — and are cured less frequently than the national norm. The NCI is addressing this troubling and complex issue through a number of activities coordinated by the Office of Special Populations Research. Some of NCI's recent activities related to special populations include:

- Developing a publication that discusses cancer's impact on special populations and describes NCI's research activities and how they affect special populations. This book is expected to be released in fall 1997.
- Convening a meeting in spring 1997 with minority leaders in the breast cancer community to discuss mammography screening, as well as future research on breast cancer.
- Working with the American Cancer Society and the Centers for Disease Control and Prevention to develop guidelines for screening for prostate cancer, a disease that affects black men in disproportionate numbers. These groups designed materials to explain to men what is known, what is not known, and what various experts believe about prostate screening, providing for a more informed choice about whether or not to be screened.
- Continuing the work of four Leadership Initiatives on Cancer — one serving black populations, two serving Hispanic populations, and one serving Appalachian communities — that research the most effective ways to convey information about cancer to those groups.

patients treated on clinical trials is much smaller (about two percent), more than 8,500 oncologists participate in NCI trials, allowing patients to benefit from advanced treatment approaches whether they are seen at the most comprehensive Cancer Center or the smallest community hospital.

Community Clinical Oncology Program (CCOP). CCOPs link community cancer specialists and primary care physicians with clinical Cooperative Groups and Cancer Centers to conduct cancer treatment, prevention, and control clinical trials. Currently, there are 51 CCOPs in 30 states, with 300 participating hospitals where some 2,000 physicians cooperate to enter patients and individuals at risk for cancer on NCI-approved clinical trials. An additional eight minority-based CCOPs are funded to enhance the participation of minority populations in clinical trials research. These programs are located in nine states and Puerto Rico, bringing an additional 42 hospitals and 350 physicians into the clinical trials network. Through this network, individuals can access state-of-the-art clinical research trials while remaining in their home communities.

Each year the CCOPs enter more than 4,000 patients into cancer treatment clinical trials (accounting for about one third of all patients on NCI Phase III treatment efficacy trials). An additional 4,000 participants are entered into cancer prevention and control clinical trials from the CCOP communities. Support is also provided for university members and affiliates to participate in prevention and control research.

The CCOP covers the spectrum from testing new combinations of anti-tumor drugs in cancer patients to testing the ability of new agents to prevent first occurrences of cancer. Examples of the latter are the Breast Cancer Prevention Trial and the Prostate Cancer Prevention Trial. CCOPs have also demonstrated successful interventions for symptom management and continuing care of cancer patients, including treatment for mouth sores and hot flashes, both common side effects of chemotherapy. The program is evolving rapidly to include interventions for individuals whose genetic profile places them at increased risk of cancer.

Training and Education

The quality and progress of the Nation's cancer research effort tomorrow will depend directly on the quantity and quality of the individuals who are attracted to careers in cancer research today, and on the appropriateness of the strategies used to train these individuals. Rapid advances in our basic understanding of genetic and molecular changes contributing to the growth and spread of cancer cells provide increasing opportunities to move this knowledge into patient and population research settings and to have a direct impact on reducing cancer incidence and mortality through new screening, prevention, diagnostic, and treatment interventions. Without adequate training, the Nation's scientific and medical workforce will be unable to bring these discoveries to the benefit of the people.

To address these challenges, the NCI's training programs support a broad range of training activities, individual fellowships and career awards, and education grants in the finest institutions in the country. NCI is currently pursuing four interdependent training and education strategies. The first is to maintain the critical mass of independent scientists studying cancer at its most fundamental levels; we know that new knowledge and discoveries in genetics and molecular biology will continue to provide the raw material from which we will develop advances against cancer. The second strategy is to encourage a greater proportion of well-trained basic scientists to expand their interests to include human biology and human disease; it is clear that the complex objectives of cancer research will depend more and more on effective collaborations between basic scientists and clinical and population scientists.

NCI's third training strategy focuses on attracting more young physicians and public health specialists into cancer research. An important effort will be to develop and sustain training programs that will markedly improve the quality and quantity of physicians trained in the clinical sciences, and to continue programs that will develop a larger contingent of physicians and public health specialists in the biostatistical, epidemiological, behavioral, and other prevention and control sciences. The fourth strategy is to use education grants to improve medical and public health curricula and to improve community education and information dissemination programs. A critical issue is how to encourage health care professionals and the lay public to make the most effective use of current information and knowledge.

To increase the number of biomedical scientists from under-represented population groups who will contribute to our advances against cancer now and into the next century, NCI continues to support extensive training and career development programs for minority individuals. NCI training programs support minority students in the pre- and post-doctoral phase of development, with awards made through the National Research Service Awards, career development awards, supplements to institutional awards, and cancer education grants. The Comprehensive Minority Biomedical Program also supports minority biomedical career development through several mechanisms, including recently developed minority medical oncology awards intended to encourage newly trained clinicians to acquire clinical research experience in oncology. Of particular importance is the emphasis the program places on issues directly related to the health status of minority populations.

A new award mechanism used to "bridge the gap" between the mentored research environment to an independent research career is the Howard Temin Award. This special award is intended for scientists who have demonstrated unusually high potential during their initial stages of training and development. It is aimed at fostering the research careers of outstanding junior basic, clinical, and behavioral scientists who are committed to developing research programs highly relevant to the understanding of human biology and human disease as it relates to the etiology, pathogenesis, prevention, diagnosis, and treatment of cancer.

NCI has also launched the Scholars Program, a career development program designed to provide outstanding young investigators the opportunity to develop their first independent research program within the supportive, interactive environment of NCI and to facilitate their successful transition to an extramural environment. NCI Scholars will independently design, pursue, and be responsible for research projects in their area of

TRAINING AND EDUCATION

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
National Research Service Awards	$41,170	$43,669	$44,419	$47,554
Research Career Program	16,898	20,973	20,486	24,003
Cancer Education Program	11,325	12,199	11,262	12,756
Minority Biomedical Research Support	1,874	3,624	2,788	3,026
TOTAL	**$71,267**	**$80,465**	**$78,955**	**$87,339**

interest. They will be affiliated with a laboratory or Branch within NCI's intramural program and will be provided with facilities, an operating budget, salaries, and personnel. After completing the three year intramural phase, successful Scholars can receive support for up to two years to continue their research away from NCI.

Resources for training are shrinking at many institutions, and some young scientists and physicians have questioned if there will be adequate support for them if they choose research careers. NCI is committed to supporting research training in the many disciplines that can contribute to understanding and ultimately solving cancer's mysteries. Strengthening the skills of basic, clinical, behavioral, and population scientists is an essential underpinning of our efforts to improve public health by reducing the burden of cancer.

Research Support Contracts

Research is a complex enterprise that can only flourish within a strong, reliable support infrastructure. The Institute uses contracts to provide support for research, information dissemination, and management.

Contracts support a variety of research activities, such as components of drug development, cancer control, epidemiology, surveillance, cancer biology, and information dissemination activities. Contracts principally support program development activities in which NCI defines the area of work, provides guidelines as to how the work will be accomplished, and establishes specific deliverables. The use of contracts is exemplified in the drug development program, where a range of services are acquired to support drug screening, synthesis, acquisition, preclinical testing, pharmacology, toxicology, and drug formulation — activities necessary to produce a new drug. The programs that employ contracts are broad and diverse, with a vital role in supporting laboratory, clinical, and population-based research, NCI's management infrastructure, and information dissemination to both the public and the scientific community.

RESEARCH SUPPORT CONTRACTS

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Cancer Biology	$72,735	$75,035	$76,288	$79,994
Cancer Risk	38,136	39,343	39,999	42,606
Cancer Interventions	120,994	124,820	126,904	135,176
Cancer Control Contracts	44,621	46,032	46,800	49,851
TOTAL	**$276,486**	**$285,230**	**$289,991**	**$307,627**

Cancer Control

Consensus among experts on the usefulness of new medical knowledge does not guarantee its widespread application. Barriers to the adoption of new medical practices may exist at many levels, including the individual, medical centers, the community, the environment, or at the interface with the health care system. The barriers may include reliance on incomplete or inaccurate information, limited access to health care services, lack of recommendation by providers, or even cultural conventions. Cancer control, as supported by the NCI, addresses these challenges through research on the behavioral, psychosocial, health services, community, and cancer surveillance aspects of translating proven techniques and tested methodologies into routine practice in the community.

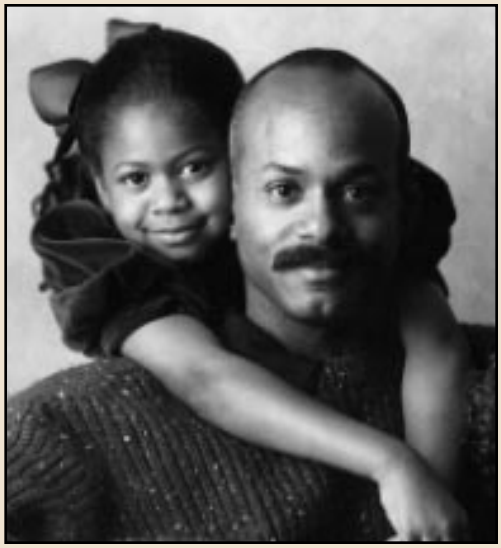
NCI's cancer control activities include a special focus on population groups who bear excessive risk for cancer or who lack access to state-of-the-art cancer services, such as minorities, low-income persons, and older Americans. Research efforts have been undertaken in collaboration with community and private sector organizations that can be mobilized to assist these population groups, and research networks of minority investigators and leadership groups of community representatives have been established. In addition, studies to assess the impact of cancer on underserved population groups are ongoing. The Black/White Cancer Survival Study, begun in 1983, investigates the effects of social, behavioral, lifestyle, biological, treatment, and health care factors on survival differences among black and white cancer patients.

Information Dissemination

Sé que el fumar causa cáncer en el pulmón. ¿Cómo puedo ayudar a mi padre a dejar de fumar?

A diagnosis of cancer catapults a family into unfamiliar territory. Shock is soon replaced by a need for answers — for complete, trustworthy information needed to make informed decisions about treatment and follow-up care. The NCI provides that information — by telephone, on the Internet, and through a wealth of printed and audiovisual materials.

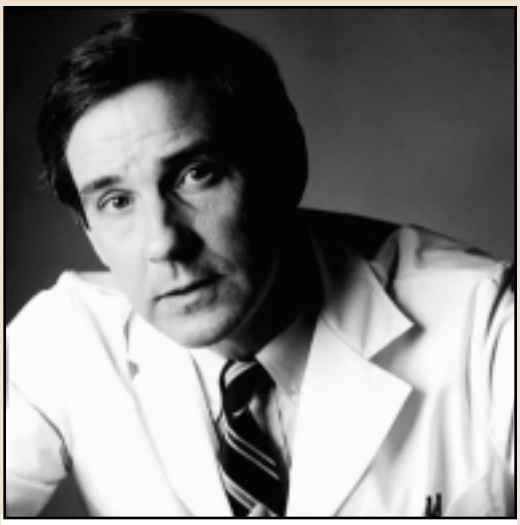
Each day, NCI's Cancer Information Service (CIS), a nationwide cancer information and referral service, receives more than 2,000 calls — from patients, their loved ones, people at risk for cancer, and health professionals — looking for help in finding the best treatment, for help with short term or late effects of treatment, for unbiased information, for support and hope. Information from the CIS also helps callers initiate health-promoting behaviors, like quitting smoking, getting a mammogram, or improving eating habits. One toll-free number, 1-800-4-CANCER (1-800-422-6237), connects callers in all 50 states and Puerto Rico with the office that serves their area. Every call is kept confidential, and trained CIS staff answer questions in English or Spanish.



The Cancer Information Service was my lifeline in a sea of medical terminology and paralyzing fear. They explained things so I could make the treatment decisions for my child that only I could make.

CIS staff will conduct customized searches of NCI's Physician Data Query (PDQ) database containing the most current information on cancer prevention, screening, treatment, supportive care, active research studies, and physicians and organizations involved in cancer care. PDQ is updated monthly and reviewed by cancer experts.

Patients with access to the Internet may also search for information about cancer on NCI's Web site **(http://www.nci.nih.gov)** or the International Cancer Information Center's award-winning CancerNet™ site (**http://cancernet.nci.nih.gov**). Health professionals can go to CancerNet for state-of-the-art cancer information, including ongoing clinical trials in which they may enroll their patients. Access to selected PDQ information is also available by fax in either English or Spanish, 24 hours a day, seven days a week, through CancerFax® (301-402-5874).



I have two patients with breast cancer, both with a strong family history. Are there genetic counselors in our area to whom I can refer these patients?

Use of these exciting communication technologies is growing rapidly, but NCI knows that most Americans still rely on the printed word for health information. Therefore, NCI makes available nearly 600 publications and audiovisual materials in Spanish and English. Designed for Americans of many cultures and literacy levels, these materials address a vast range of cancer-related topics — from coping with the emotional burden of cancer, to lowering the fat content of traditional ethnic foods, to understanding clinical trials.

To meet the growing demand for up-to-date cancer information, NCI is continually exploring the latest technologies, optimizing community partnerships, and pursuing entrepreneurial ventures that will expand awareness and access while maintaining our "gold standard" of providing individualized service and the best information possible.

CANCER CONTROL

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Grants	$61,158	$70,133	$76,488	$89,450
Contracts	110,152	105,911	116,539	123,492
Research Support	44,877	55,664	47,321	50,659
TOTAL	**$216,187**	**$231,708**	**$240,348**	**$263,601**

The study includes patients with breast, colon, uterine, and bladder cancers. NCI is also conducting two large studies of risk factors for prostate cancer, one among U.S. black and white men at high risk and one among low risk Chinese men in Shanghai. These two studies investigate genetic, biochemical, behavioral, and environmental factors that may affect the occurrence of prostate cancer.

Cancer surveillance is a critical component of cancer control and, in fact, underlies the entire NCI research portfolio. Tracking and analyzing trends in cancer incidence, mortality, and survival rates stimulates new activities and allows us to monitor the effects of ongoing programs. The cornerstone of this effort is the Surveillance, Epidemiology, and End Results (SEER) Program, which monitors the Nation's cancer burden and provides the basis for assessing individual, organizational, and societal factors that can reduce cancer rates.

Spreading the Word: The NCI's Information Dissemination Mandate

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate. NCI's programs in communications, education, and outreach are based upon needs identified through epidemiologic studies and market research among specific population groups. This allows the design of programs that are relevant and understandable to each group. The NCI's patient education program, leadership initiatives for special populations, and minority research networks are all actively involved in spreading state-of-the-art information about cancer prevention, detection, diagnosis, treatment, and care.

The primary avenues NCI uses to communicate with the public and the health care community are:

World Wide Web: NCI's Web site can be found at http://www.nci.nih.gov. To fully realize the enormous information dissemination potential of the World Wide Web, the NCI is currently redesigning its Web site to increase its usefulness as a communication tool. The new Web site will be organized so that clinicians, researchers, and the public can quickly and easily locate up to-the-minute information that is relevant to their needs.

Many NCI offices and laboratories already maintain their own Web sites. In addition, the NCI Intranet, a special Web site accessible to NCI staff only, facilitates information sharing among scientists at the Institute.

The Cancer Information Service (CIS): The CIS provides accurate, up-to-date cancer information to patients and their families, the public, and health care professionals in every state through 19 offices located at NCI-funded Cancer Centers and other health care institutions. By dialing 1-800-4-CANCER, callers are automatically connected, free of charge, to the office serving their region. Information on specific cancer types, state-of-the-art care, clinical trials, and resources such as support groups or screening and smoking cessation programs is provided in English or Spanish by specialists who respond to more than 600,000 inquiries annually. CIS offices catalog local cancer-related services, catalyze community outreach efforts, and provide print materials and technical assistance to help local organizations sponsor cancer education programs, media campaigns, and other community programs. The CIS regional offices are also NCI's focal point for state and local cancer education efforts that target underserved, high risk, and low literacy populations.

The International Cancer Information Center (ICIC): The ICIC provides an array of cancer information for scientists, health care professionals, and the public. ICIC staff are responsible for developing and maintaining PDQ, the NCI's comprehensive cancer information database, as well as the bibliographic CANCERLIT database. ICIC also maintains the CancerNet™ Web site (http://cancernet.nci.nih.gov), a repository of current cancer related information, including selected PDQ information, NCI Fact Sheets for patients and the public, and news and information from the cancer community.

Selected PDQ information, NCI Fact Sheets, and other materials are available in Spanish and English 24 hours a day, seven days a week through NCI's CancerFax® facsimile system, and via Internet electronic mail. All of the ICIC's scientific information services are available through its innovative Information Associates Program, a customer-oriented membership service launched in 1994.

HIV Drug Resistance Program

One of the most frustrating aspects of treatment for HIV infection and AIDS is that eventually, the drugs stop working. Individual drugs can hold the virus at bay for a while, but at some point, the virus mutates in a way that renders it impervious to the treatment. This phenomenon is known as drug resistance. New regimens, led by the promising new class of drugs known as protease inhibitors, have made enormous headway in eliminating drug resistance, but the long term efficacy of these regimens is not yet known.

Solving the problem of drug resistance is the primary mission of a brand-new NCI-led effort, the HIV Drug Resistance Program at NCI's Frederick Cancer Research and Development Center. Drawing on NCI's already strong program of AIDS-related research, the new program will integrate existing and newly formed groups of investigators from numerous disciplines; the expertise of investigators at other institutes at the National Institutes of Health will also be called upon. Through a program of cutting-edge basic, translational, and clinical research, the HIV Drug Resistance Program is expected to become a center of excellence in this extremely challenging area of AIDS and HIV research.

AIDS Research

Malignancies complicate more than 30% of AIDS cases and contribute a great deal to AIDS morbidity and mortality; many areas of fundamental biology developed in NCI programs, including virology, immunology, and cell and molecular biology, are directly applicable to understanding HIV and AIDS. Today, research into the fundamental biology of HIV and AIDS, AIDS treatment, and particularly AIDS-related malignancies takes place throughout all programmatic mechanisms of NCI.

The NCI Intramural Research Program has been an important, internationally recognized center for research in HIV and AIDS, producing important discoveries about HIV, pediatric and adult AIDS, AIDS malignancies, and AIDS therapeutics.

Among the NCI Extramural Program's achievements in AIDS research are:

- An AIDS Malignancy Consortium that brings together researchers, clinicians, and relevant support facilities at 13 institutions throughout the country to foster interdisciplinary research on AIDS-associated malignancies and translate laboratory discoveries into new clinical interventions.
- An AIDS malignancy tissue bank that provides resources for testing hypotheses about the development, progression, and response to therapy of these cancers.
- AIDS malignancy initiatives in NCI's clinical trials programs.
- Epidemiologic and surveillance studies that provide invaluable resources for tracking HIV, AIDS and, in particular, AIDS malignancies.
- An AIDS Malignancies Working Group that met during 1996-97 to assess progress to date in AIDS malignancies research, identify and prioritize important research opportunities and approaches, and recommend future research directions.
- The National AIDS Malignancy Conference, held in April 1997 to discuss progress and stimulate research across diverse disciplines.
- AIDS/Oncology Clinical Research Training under the Clinical Scientist Development

RESEARCH MANAGEMENT AND SUPPORT

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Research Management and Support	$100,831	$99,957	$100,793	$108,820

OTHER RESEARCH SUPPORT

(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Core Budget
Scientific Evaluation (U09)	$4,534	$4,784	$5,234	$7,001
Resource Grants (U24)				3,000
Construction	3,000	3,000	2,573	5,000
Conference Grants	954	1,104	705	1,100
Continuing Education	114	214	560	626
TOTAL	**$8,602**	**$9,102**	**$9,072**	**$16,727**

Program Awards, will support institutional, multidisciplinary training programs focused on the AIDS oncology field.

NCI's research programs have been at the forefront of progress against AIDS since the epidemic was first identified. The NCI, in coordination with all of the other Institutes and the NIH Office of AIDS Research, continues its commitment to meeting the challenge of AIDS and is working to ensure integration of NCI-supported AIDS and AIDS-related research with national AIDS strategies. AIDS research dollars are distributed throughout the budget.

Research Management and Support

Research Management and Support includes activities essential to sustain, guide, and monitor both the extramural and intramural activities of NCI. These activities include overall scientific program direction and administration by the Office of the Director, with assistance from grant and contract science managers, finance, human resource, legislation, science program direction and assessment, and technology transfer staff. The review and oversight activities of the National Cancer Advisory Board and President's Cancer Panel are also included. This part of the budget also supports NCI's share of central NIH facilities and operations, and extramural staff salaries (intramural staff salaries are included under the Intramural Research budget, as is intramural facilities maintenance).

Other Research Support

This area incorporates smaller grant activities such as Conference Grants, Scientific Evaluation, and construction grants and contracts. Conference grants support meetings, conferences, and workshops relevant to promoting the goals of NCI. Scientific Evaluation awards are the vehicle that supports the scientific review of grant and contract proposals. The grant reviews are conducted by either the NIH Division of Research Grants or the NCI, depending on the granting mechanism. Construction funds provide partial support for the modernization or development of cancer research facilities at institutions located throughout the Nation. Additionally, limited construction funds are provided for repair and development at the Frederick Cancer Research Center.

Extraordinary Opportunities for Investment

Progress in cancer research involves foresight, creativity, planning, hard and exacting work, serendipity, and, most critically, recognizing and acting on promising research opportunities at key points in time. Since the National Cancer Institute was formed in 1938, we have established a multifaceted research program, a discovery process that has enabled us to open many doors and make tremendous strides forward in our understanding of cancer and how to prevent, detect, diagnose, and treat it. Yet we still have much to learn and much to do to alleviate the burden of cancer. We have reached a critical juncture at which we must again ask ourselves, "What will it take for us to move forward?"

The answer is twofold. First, we must continue to support the vital research that has brought us this far; second, we must recognize extraordinary new opportunities for further progress and invest in them. Although research is often driven by need, our history has taught that being prepared to seize research opportunities is the best way to meet those needs.

With these challenges before us, in 1996 we began a process of looking critically at the field of cancer research and selecting areas of discovery with exceptional promise for achieving pivotal advances in our knowledge about cancer and in benefits for patients and those at risk for cancer. We identified four avenues of discovery with the potential to change the face of cancer research and cancer care. These "Extraordinary Opportunities" for immediate investment in cancer research are:

- Cancer Genetics
- Preclinical Models of Cancer
- Imaging Technologies
- Defining the Signatures of Cancer Cells: Detection and Diagnosis

How can we best seize the many opportunities that flow from these diverse scientific areas? During the past year, NCI has begun to move forward in each area through our intramural and extramural research programs. But to take full advantage of the enormous potential these opportunities offer, we need a more focused effort and an infusion of funds. Although the resources required are not trivial, investing now will yield tremendous benefits in the future. The knowledge we gain will lead to new and better prevention, detection, diagnosis, and treatment techniques.

In the following pages, we describe how these four extraordinary opportunities were selected, the broad goals and objectives for each opportunity, how we are laying the foundation for success, and when we will reassess these opportunities. We then discuss each area of opportunity in detail, describing its specific goals, research opportunities, plans, progress to date, and the consequences of not investing.

Setting Priorities: Criteria and Selection Process for the Extraordinary Opportunities

What makes an "extraordinary opportunity" different from the many other important areas of research supported by the NCI? The four initiatives identified as extraordinary opportunities meet several important criteria. First, they respond to important recent changes or developments in knowledge and technology in all aspects of cancer research. Second, these opportunities offer approaches to cancer research that go beyond the size, scope, and funding of our current research activities. Third, they can be implemented with specific, defined investments. Fourth, the initia-

tives can be described in terms of achievable milestones, with clear consequences for not investing. Fifth, they promise advances that are needed for making progress against all cancers. Finally, each of these ripe investment opportunities address needs at the interface between basic and clinical advances — so-called translational research.

We identified these areas for investment through a simple process. In discussing the state of cancer research with scientists, educators, advocates, and community leaders, we asked them — and ourselves — two difficult questions: "Where are we failing?" and "What must we do to succeed?" We found that our most serious deficits have been primarily ones of omission; that is, where we are failing to fully pursue promising leads. These discussions also highlighted areas in which a critical mass of knowledge had been attained so that significant new initiatives could achieve remarkable new insights and discoveries.

During a six-month period, 60 different proposals for new opportunities were put forward. As the subjects of these 60 proposals were explored, analyzed, and refined, we realized that they were often different views of the same issues. Related meritorious ideas were blended together to create the list of four opportunities that captured the best aspects of the many proposals. They are, in many ways, new doors to discovery that have been opened by past successes. Other investment opportunities can be formulated and all opportunities will be re-examined on a three-year cycle.

Opportunities: Objectives and Goals

For the four extraordinary opportunities ready for investment, additional resources will enable NCI to accomplish the following:

Cancer Genetics —

Objectives: Expand and integrate basic, clinical, and epidemiologic research, facilities, and training in cancer genetics to identify and characterize genes responsible for inherited predisposition to cancer; develop diagnostic tests for alterations in these genes; provide training in genetic counseling and in cancer genetics for health professionals; develop the informatics needed to collect, store, analyze, and integrate the resulting molecular, epidemiologic, and clinical data; and educate the public and high-risk persons about cancer genetics.

Goals: Identify every major human gene that predisposes people to cancer; use the knowledge we gain as we identify these genes to help patients at risk; and deal with the psychosocial, ethical, and legal issues associated with inherited cancer susceptibility.

Preclinical Models of Cancer —

Objectives: Develop new preclinical models of cancer to study gene mutations important in human cancers; provide a natural setting for studying all stages of tumor development; and facilitate more rapid testing of cancer prevention and detection strategies and new treatment regimens.

Goals: Create animal models of human cancers; build the experimental foundation to use these models effectively; and develop the infrastructure and procedures needed to make these models available to all researchers.

Imaging Technologies —

Objectives: Improve diagnostic imaging technology so that it is both sensitive and specific enough to detect very small numbers of tumor cells.

Goals: Discover and develop techniques that will further increase the precision, accuracy, and scope of imaging diagnosis; and integrate imaging further into the practice of clinical oncology.

Defining the Signatures of Cancer Cells: Detection and Diagnosis —

Objectives: Improve the early detection of cancer by identifying in body fluids tumor-specific secreted proteins and mutant genes that may signal the presence of small numbers of pre-malignant or malignant cells; use new knowledge of the molecular traits of tumor cells to improve our ability both to diagnose cancer and to choose effective therapies and plan patient care.

Goals: Develop new methods for detecting tumors at their earliest stages, when the number of tumor cells is small and the chance for cure or control is greatest; develop diagnostic tests that will enable treatment choice to be based on the fundamental properties of a tumor cell that determine the course of its development.

Laying the Foundation for Success: Activities in FY 1996 and 1997

The foundation for the success of these four opportunities will be built on the body of work amassed over the years by researchers in the laboratory, the clinic, and the community. To fully exploit their exceptional potential for progress, we must increase and concentrate our efforts. During FY 1996-97, NCI has paved the way for capitalizing on these opportunities through a planning process fueled by the expertise of a unique group of advisory committees, the NCI Director's Working Groups.

The Working Groups are ad hoc, scientific think tanks appointed to examine key scientific areas of importance to NCI. Their members include leaders in laboratory, clinical, and population-based research drawn from the extramural and intramural research communities, NIH and other government agency staff, members of professional organizations, and consumer and patient advocates. We established the Working Groups to help us transform the broad goals discussed in last year's budget document into realistic plans with short-term and long-term scientific aims and objectives, including implementation strategies and milestones for measuring progress.

Recommendations resulting from Working Group discussions provide a framework for strategic planning in each opportunity area and for the development of operational plans by NCI divisions. These plans will result in new extramural grant or contract awards; collaborative efforts with other Institutes, government agencies, or the private sector; and new or expanded scientific programs within the divisions at NCI.

Two of these Working Groups, Cancer Genetics and Developmental Diagnostics, met several times in 1996. Their recommendations resulted in exciting initiatives such as the Cancer Genome Anatomy Project that promise to advance the science rapidly in these areas. The other groups, formed more recently, are in the early planning stages. For this reason, our plans in some groups are more detailed than in others.

Reviewing and Recasting Opportunities: A Three-Year Cycle

Our knowledge and understanding of cancer are continually evolving. Many of the treatments and techniques that revolutionized cancer research and cancer care 25, 15 — even five years ago — are considered routine today. Older treatments have been replaced by newer, more effective, and often less toxic therapies — the result of investment in research. Similarly, we expect that the current "extraordinary" opportunities will produce the future standards of practice, and will then quickly be replaced by new opportunities as scientific discoveries continue to occur.

Therefore, we have begun a three-year cycle for revisiting and recasting current investment opportunities and identifying emerging opportunities with the greatest potential for making progress against cancer. During each cycle, we will actively seek research opportunities that arise from important new discoveries and meet other agreed-upon criteria. We expect these new opportunities to come from many sources, including review groups, the scientific and advocacy communities, NCI program staff, and our constituents. However, the cycle of discovery, as with any enterprise, cannot begin without the initial investment that will enable us to pursue fully the opportunities now at hand.

OPPORTUNITY 1
Cancer Genetics

Years of intensive research have enhanced our understanding of how tumors develop. Foremost, we have learned that cancer is a genetic disease. Alterations in our own genes or their products, whether inherited or acquired, drive the development of cancer. These mutations alter the normal processes that a cell uses to regulate its actions. When these processes are disrupted, control is lost and tumor development is promoted. A cancer will arise only after several mutations occur in the

same cell. One mutation is never sufficient; multiple mutations are required to generate the full set of changes that make tumors aggressive. These accumulated mutations give growth and survival advantages to the tumor cell and allow the cells to multiply out of control. They divide, obstruct, invade, and destroy normal tissue architecture. Through the accumulation of genetic changes, these cells acquire properties that allow them to escape the normal biological defenses and controls and go on to pose a life-threatening problem to the individual in whom they live.

We also have learned that the number of different genes that can be mutated and contribute to the many types of cancer is large — most likely in the hundreds. These numbers are large, daunting perhaps, but not impossible to manage.

The most direct and ultimately the most effective approach to preventing, detecting, diagnosing, and treating cancer is to identify the traits of the responsible genes. Recent advances in our understanding of human genetics have provided an important new opportunity to identify cancer genes through studies of cancer-prone families; in just the past seven years, more than 20 such genes have been discovered in this way. This approach unlocks vast potential to expand our knowledge of the origins of cancer, to develop new ways to detect a tumor in an early stage, and to identify new targets for cancer therapies. With this opportunity, however, comes an important social responsibility to provide effective and helpful genetic counseling and protect the confidentiality of personal genetic information. Our plan to extend our knowledge and use of cancer genetics addresses scientific discovery, clinical research, medical application, and social responsibility.

The Goals

1. Identify every major human gene that predisposes people to cancer.
2. Begin to apply these discoveries through clinical practice to help patients at risk.
3. Identify and address psychosocial, ethical, and legal issues associated with inherited cancer susceptibility.

The Opportunity

Recent discoveries have ushered in a new era in cancer research. We have long known that it is important to identify risks that predict an individual's likelihood of developing a particular cancer and have even longer recognized that cancer may "run in families." For certain cancers, we now are able to identify in cancer-prone families the specific genes that predict an individual's risk for cancer.

The most successful approach to identifying human "cancer genes" (genes whose alterations predispose to cancer) has been to use the tools of human genetics. About 10 percent of all cancers in the United States occur in individuals who have inherited a mutation that predisposes them to cancer. Several million Americans carry such inherited predispositions. The likelihood that a tumor will develop can be predicted to an extent by the rules of heredity. In cancer-prone families, for example, genes passed from one generation to the next influence the chance of developing a tumor.

Tracing patterns of inheritance has provided an important method for studying cancer by giving scientists the molecular signposts that identify where to look for cancer genes. By studying families with a strong cancer history, we can gather the clues that will enable us to identify other culprit genes. Scientists have learned that the same genes that predispose members of cancer-prone families to disease quite often also contribute to the development of cancers in individuals with no family history. We now realize that there are not two different sets of cancer genes, one group for inherited predisposition and one for sporadic (uninherited) tumor development. The mutations that result in inherited predisposition are a subset of the ones that spur all human tumor development. Therefore, using the rare predisposition genes to learn more about common cancers is a promising research strategy, and the cancer genetics initiative proposes a plan to take full advantage of this knowledge.

It is also true, however, that most diseases and traits don't follow simple patterns of inheritance; a variety of factors may influence a gene's effect. Identifying the factors that determine when a particular genetic mutation will lead to cancer and

when it won't is a crucial part of our intensified efforts in cancer genetics research. We also are learning that cancer risk can be modified even in individuals who carry cancer-predisposing genes. Other genetic and environmental factors that influence the development of cancer in these high-risk individuals are also likely to provide valuable insights about cancer development in the general population.

Numerous lifestyle and environmental carcinogens have been identified by investigating cancer in populations (epidemiology), and this knowledge has led to new approaches for reducing cancer risk. But there is still much to learn about the causes of cancer, particularly why one person with the same cancer-causing exposure (such as smoking) develops cancer, while the other does not. New genetic discoveries and technologies are having a dramatic impact on our ability to explore gene-environment interactions that may account for differing susceptibilities in the general population. By applying advances in molecular genetics to population-based studies, it is possible to identify common genetic alterations that contribute to cancer risk. For example, researchers found that approximately half the population lack a common gene that helps to detoxify cancer-causing chemicals in cigarette smoke, a trait that places this group at higher risk for smoking-related cancers of the lung and bladder. Ideally, this information could be used to alert patients to their risk for developing these cancers. In addition, there is growing evidence that the pattern of mutations detected in certain tumors may be distinct enough to provide a molecular fingerprint traceable to specific environmental agents.

Large, population-based studies are being conducted to evaluate cancer risks associated with the combined effects of genetic status and environmental exposures, including those related to lifestyle and diet. Using minute quantities of DNA in cells obtained from a simple mouth rinse, blood, or tissue, it is possible to detect gene mutations whose functions or effects may point the way to environmental, nutritional, hormonal, and other factors that contribute to cancer. As more information about human genes becomes available, there will be striking opportunities to test the importance of newly discovered genes not only for their relation to cancer susceptibility, but also for clues to environmental carcinogens. The tools to examine these complex interactions between genetic susceptibility and environmental exposures are being developed for studies that could greatly advance our understanding of how inheritance, lifestyle, and environment combine to cause cancer. This knowledge will lead to new strategies for cancer prevention.

The opportunities afforded by advances in cancer genetics also raise enormous challenges. What clinical, medical, and surveillance issues arise from being able to determine inherited risk for cancer? What are the psychological, social, and family consequences? The cancer genetics investment initiative also must ensure that individuals are helped, not harmed, by personal genetic knowledge.

The Plan

To capitalize on these unprecedented opportunities and to meet the diverse challenges in cancer genetics, support is needed for new activities in a number of areas:

- We need to support the identification of high-risk families and the multidisciplinary research infrastructure required to identify and characterize cancer predisposition genes.

- We must make available to clinical researchers the technology and resources they require to detect gene alterations and ensure that these alterations can be reliably and effectively measured.

- Resources, including appropriate study populations and biospecimen collections, must be increased significantly for clinical and epidemiological research to answer key questions about inherited mutations in cancer susceptibility genes. For example, what is the cancer risk for individuals who inherit different mutated forms of a particular cancer gene? Are there effective surveillance and detection strategies to monitor for early signs of cancer? By integrating clinical, laboratory, and population-based applications, it will be possible to

develop more precise and effective strategies designed to prevent cancer, improve care, and address the ethical and psychosocial issues related to genetic testing.

- Support is needed for training and the development of educational programs aimed at the public, people at high risk for cancer, health care providers, and payers to help them understand the enormous importance of genetics in oncology. A recent survey of primary care physicians found that most are not prepared to deal with genetic information. As the volume and impact of genetic information increases, a medical work force with expertise in genetics and counseling is required, and this must be achieved quickly.

- We need to develop an informatics system to collect, store, analyze, and integrate molecular data with epidemiologic and clinical data. Several parts of the cancer genetics initiative will involve generating and analyzing massive amounts of data about dozens of genes and hundreds of possible alterations in each gene. Data on these gene alterations must be correlated with disease outcomes. These complex activities cannot be accomplished without a dynamic and accessible informatics infrastructure that allows a new level of exchange across scientific disciplines. It is also of the utmost importance to design a secure system that protects the confidentiality of all collected data.

- New techniques in molecular genetics must be combined with more powerful statistical and epidemiologic approaches to investigate gene-environment interactions and their influence on cancer risk. By correlating our growing knowledge of the biological mechanisms that allow individuals to respond to the environment with detailed knowledge of genetic variation among individuals, we can begin to identify those individuals who are constitutionally susceptible to particular environmental exposures. This can help to identify people at high risk who may benefit from special interventions.

Together, these areas of the cancer genetics initiative provide a unique opportunity to attack the cancer problem at its core with speed, coordinated effort, and insight. With a national effort in this area, opportunities for key scientific advances will be gained, cancer care advances will be made more rapidly, and difficult psychosocial and societal issues will receive the timely attention they require.

Progress in Pursuit of Our Goals

As the first step in planning a coordinated national cancer genetics program, a group of outstanding scientists, the Cancer Genetics Working Group, was convened to discuss research opportunities and barriers to scientific progress. A new initiative, the Cancer Genetics Network, resulted from these discussions. The Network, a dynamic informatics infrastructure linking participating centers that counsel, test, and monitor individuals for cancer susceptibility, will be launched during this fiscal year. The Network will provide a platform for genetics research and support the development of critically needed educational resources. Ultimately, the Network will help to answer important questions, such as whether preventive surgery reduces mortality for people who have altered cancer susceptibility genes. This initiative will complement existing NIH-supported programs, increasing the access of individuals at risk for hereditary cancers to counseling and genetic testing within a research setting. The Network also will enable NCI to rapidly launch critically needed studies in this area.

In 1996, to foster new genetics research and genetics counseling/education in the cancer research community, NCI solicited proposals from NCI-designated Cancer Centers for innovative projects in these areas. NCI provided supplemental funding for over 50 projects and resources addressing either heritable factors affecting cancer susceptibility in humans or genetic counseling/education approaches. Results from these short-term projects should provide a springboard for more extensive research studies and contribute valuable information for planning initiatives through a variety of funding mechanisms.

To meet the swiftly growing need to educate health professionals and the public about genetic testing and its implications, in the next year NCI will invite proposals for education and training programs in genetic counseling. The aim of this effort will be to support projects that develop new educational materials or use existing materials in innovative ways to inform health professionals in training, oncology physicians and nurses, genetic counselors, or individuals at high risk for cancers known to have a substantial genetic component. An important aspect of these projects will be to deal with cultural issues and barriers associated with genetic counseling among ethnic minority populations.

Consequences: Investing versus Waiting

The era of genetic medicine is upon us. The plan outlined above is designed to complete the identification of all major cancer susceptibility genes within five years and to participate in preparing our Nation and its health care system

IMMEDIATE OPPORTUNITY

Genetic Testing for Cancer Susceptibility: An Opportunity and a Challenge

"Will I get cancer?" Although we can't answer this question with certainty for any individual, we do know that a small subset — perhaps 10 percent — of the population carry inherited alterations in their genes that place them at a substantially increased risk. Hereditary genetic alterations are implicated in some cancers of the breast, prostate, colon, kidney, and ovary, as well as in other, less common, types of cancer. In addition, hereditary cancer syndromes such as Li-Fraumeni and von Hippel-Lindau can afflict numerous family members across multiple generations.

Tests to determine whether someone carries a genetic mutation rendering them susceptible to cancer are becoming increasingly available. While these tests are useful and appropriate in many instances, they also have serious, sobering limitations. Cancer results from a complex interplay between genetic, environmental, and other factors. Even when a test reveals that a person's risk of getting cancer is very high, the risk is not absolute; likewise, a negative result does not guarantee that the testee will never get cancer. A positive result for a cancer susceptibility mutation can have profound psychological, social, and even legal consequences. We still do not have sufficient research data to address effectively the troubling ethical, legal, psychological, and social issues raised by gene testing. The most serious limitation to gene testing, however, is the fact that test information is not matched by knowledge on how to prevent the cancers or lower risk of dying from them.

The NCI is responding to the challenges posed by genetic testing through these initiatives:

Cancer Genetics Studies Consortium. Co-sponsored by the NCI and the National Human Genome Research Institute, the Cancer Genetics Studies Consortium, a group of NCI-funded research centers, examined testing and counseling methods for susceptibility to colon, breast, and ovarian cancers. Some of the centers' grants are being renewed, and some will receive supplemental funding to study counseling and testing for *BRCA1* mutations in the Ashkenazi Jewish population.

Familial Cancer Registries. The NCI supports a number of familial cancer registries, which provide an infrastructure of cancer-prone families in whom research about behavioral/psychosocial issues related to genetic testing can be conducted. Registries for breast cancer and breast-cancer related syndromes (for example, Li-Fraumeni Syndrome), ovarian cancer, and colorectal cancer are ongoing.

Cancer Genetics Network. The Cancer Genetics Network will provide us with another platform for behavioral and psychosocial research related to genetic testing, as well as the opportunity to answer questions about the nature of various prevention and early detection strategies for those with identified mutations. (See page 54.)

Education and Outreach. Recognizing the importance of accurate consumer information on this complex topic, NCI has issued an informational booklet entitled *Understanding Gene Testing.* This booklet is meant for the general public, as well as people who are considering genetic testing, and is available through the Cancer Information Service at 1-800-4-CANCER. In addition, NCI is working in partnership with the National Action Plan on Breast Cancer to produce a brochure and videotape on genetic testing for breast cancer susceptibility.

CANCER GENETICS RESOURCES

	FY 99
MAP AND CLONE ALL MAJOR HUMAN CANCER SUSCEPTIBILITY GENES	**$4.35M**
• Initiate project to map and clone cancer genes (10 genes/year)	
• Develop informatics associated with this effort	
GENE-GENE INTERACTIONS: IDENTIFICATION OF MODIFIER GENES	**$7.5M**
• Initiate project to identify modifier genes (five modifiers/year)	
• Assess human homologues for correlation with familial cancers	
GENE ENVIRONMENT INTERACTIONS: MOLECULAR EPIDEMIOLOGY	**$10.0M**
• Collect and maintain population-based repository of biological specimens	
• Measure exposure to environmental risk factors	
• Develop and employ questionnaire for environmental risks	
• Develop informatics associated with this effort	
CANCER GENETICS NETWORK	**$6.0M**
• Establish initial members of network	
• Develop informatics associated with the Network	
SUPPORT FOR BREAST AND COLON CANCER FAMILY REGISTRIES	**$0.85M**
• Develop informatics center linking registries	
COMPREHENSIVE MOLECULAR ANALYSIS	**$25.0M**
• Establish six Technology, Development and Resource Centers	
• Conduct five pilots in comprehensive molecular analysis (breast, colon, prostate, lung, ovarian)	
• Identification and cloning of genes implicated by above pilot studies	
• Develop database of chromosomal aberrations in cancer	
• Create a BAC library representing chromosomal breakpoints and translocations in cancer	
CANCER GENETICS TOTAL	**$53.7M**

to embrace the benefits and address the potential pitfalls of genetic medicine. The consequences of not establishing a national cancer genetics plan are dire. In the absence of this investment, we will not be able to respond to individuals who want to know whether they are at increased risk for cancer due to an inherited predisposition. Without this investment, we may be unprepared for the ethical, legal, and other challenges associated with testing. Without this investment, we will be unable to answer the questions health care providers and individuals will have about what to do with this potent information. Without this added investment, we will be unable to offer participation in important clinical trials and careful counseling to millions of Americans who will seek guidance and answers. Finally, without this added investment, we will not be able to utilize fully and rapidly the advances in cancer genetics to improve our understanding of cancer and loosen its grip on the Nation.

Missing this opportunity will slow the pace of all levels of research, and many people who could have been helped will not be. Ultimately, we will have missed new possibilities for prevention, early detection, and treatment. This is a pivotal opportunity to provide leadership in addressing the fundamental societal issues that accompany genetic testing. We are quickly approaching an era when genetic testing will be widely available. Already, tests for certain gene mutations are available outside the research setting, and the benefits and drawbacks of using them are hotly contested. By establishing a clear, integrated plan, we will be able to pave the way for the ethical use of genetic testing and provide the basis for responsible growth and development. The cancer genetics initiative offers a plan to make the most of our recent discoveries and, as importantly, to generate new ones.

OPPORTUNITY 2
Preclinical Models of Cancer

We have gained substantial ground in our assault on the mountainous problem of cancer. Our research and discovery process has identified an initial array of important cancer genes, and we are now poised to discover all of the genes that, when mutated, contribute to human cancers. As crucial as we know this work to be, we also know that we must go beyond simply identifying these cancer genes — we must understand how changes in these genes contribute to the transformation of a normal cell into a life-threatening cancer. What is the gene's normal role in the cell? How does a mutated version of the gene function? How does it interact with other known cancer genes? We know these are critical questions that must be answered to achieve major advances in cancer research. Yet the study of cancer genes and how they change the properties of normal cells has been limited by the types of experimental systems or settings available for such studies.

To find these answers, we need to manipulate genes in a living system and then study the biological effects of the alterations we introduce. For both technical and ethical reasons, we cannot perform these studies in humans; therefore, we need experimental models that mimic human disease. New techniques have enabled us to modify the genetic makeup of animals and simple organisms to serve as preclinical models of human cancer, facilitating both basic science investigations and the testing of promising preventive or therapeutic agents. This technology will be used responsibly, and the NCI is committed to the humane care and use of animals in research. These models will be extremely important to us, allowing us to study and understand cancer in ways that were impossible even a few years ago.

For example, new advances in mouse genetics offer the opportunity to study tumors in a natural mammalian setting that accurately parallels human cancer development. Before this new technology, we could not make animals susceptible to specific cancers via the same genetic predispositions now known in humans. Researchers can now alter mouse genes and introduce the same mutations that occur in human cancer. These mutant mice predictably develop specific cancers and pass these susceptibilities to their offspring in the same way that humans may inherit a predisposition to a particular type of tumor. With these models, we can examine every stage of tumor development, from the very early stage when a tumor first appears to the advanced stages when the tumor spreads to distant sites within the body. Moreover, these mouse strains provide previously unavailable settings for testing the vast number of new approaches for cancer treatment or prevention that are in the developmental pipeline.

Models using even simpler organisms like flies, worms, and even baker's yeast are other powerful examples of how we can learn about human cancer by studying non-human systems. In these simple organisms we have found biological systems we can use to understand how cells make the decision to divide or not. Since cancer cells grow and divide in an uncontrolled way, a detailed understanding of cell division is critical to understanding cancer. We know that many of the cancer genes already identified play a role in cell division, and now we have the opportunity to use these relatively simple and easily manipulated biological systems to determine how the mutations that cause cancer force cells to divide at inappropriate times.

These are only a few of the opportunities for which model systems can be created to further our understanding of cancer and hasten our progress in developing new methods for detection, diagnosis, and treatment. The applications of these technologies may be virtually limitless.

The Goals

1. Create models of tumor development in mice based on our knowledge of human cancer genes and use these models to study the biology of tumor development.

2. Use the mouse models of tumor development to study methods of cancer intervention: (a) test potential strategies for preventive interventions to block the development of tumors; (b) analyze new methods to treat tumors after they have developed, and

(c) establish the best approaches for early cancer detection and diagnosis.

3. Use simple organisms that can be manipulated as tools for discovery to help understand the normal role of human cancer genes and to determine both how cells make decisions to divide and how cancer cells lose the ability to make these decisions correctly.

4. Develop the infrastructure and procedures needed to make these models available to all researchers.

The Opportunity

In the laboratory we have been able to identify a number of the mutations that drive cancer formation, and we now have a growing understanding of how these mutations trigger the initial steps in tumor development. The better we understand these steps as a normal cell progresses to a tumor cell, the better we will be able to develop interventions than can block the progression. But the study of these mutations and how they change the properties of a normal cell has been limited by the types of experimental settings in which we could examine these changes. Our inability to establish model systems to study the great variety of human cancers, their development, and their progression has been a major roadblock to the discoveries needed to reduce the cancer burden in people.

This roadblock has now been overcome by several recent advances that have led to unprecedented opportunities for:

Sudying cancer mutations in a living organism. Using techniques developed through NIH support, investigators can now insert any mutation or combination of mutations into the genetic material of a mouse. These mice provide a natural setting to study all stages of tumor development and the impact of multiple genetic events at each stage. Understanding the early stages of tumor development will help us develop better tools for detection and diagnosis. Also, these animal models will be particularly important for studying the complicated later stages of tumor spread and invasion, areas of research that deal with the most threatening aspects of human cancers.

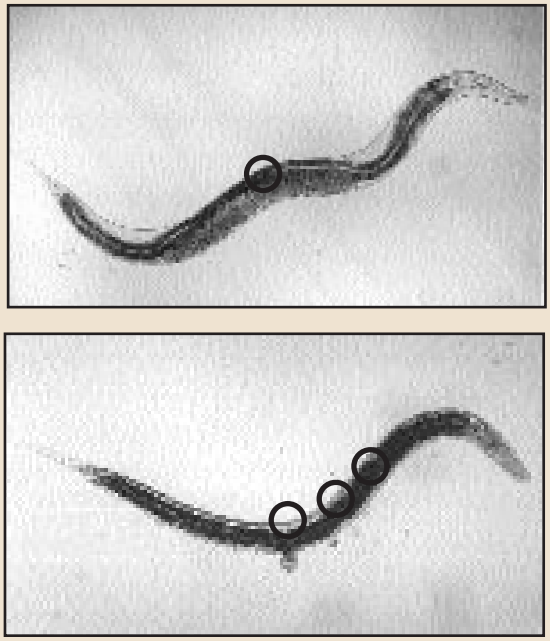
Identifying new cancer genes. Our knowledge of the number and type of genes that contribute to cancer is still growing. Using animal models, we can identify new cancer genes at a faster pace. Two approaches seem most fruitful. In the first, we can genetically introduce the mutations involved in the first steps of cancer development, and then let the next steps of tumor development proceed. Tumors that result can be analyzed to identify the new mutations that have occurred. This approach may be the best way to identify and understand other genes and environmental and dietary factors that affect cancer development and progression. A second approach to identifying new cancer genes takes advantage of the existing large number of abnormal mouse strains that develop tumors. With NCI support, these mouse strains are currently being analyzed to determine their different tumor profiles (i.e., what tumors commonly occur in a given strain). With this information, we will be able to move forward to identify the mouse genes responsible for generating the tumors.

Applying knowledge of non-mammalian genetic systems to the study of human cancer. As each new cancer gene is discovered, we need to determine why its mutation can lead to cancer. One approach to learning this is to study a relative of that human cancer gene in a model system where its normal role can be determined more easily. The fly, worm, and yeast versions of several human cancer genes appear to behave similarly to the human genes. These organisms will help us understand human cancer by providing accurate models that are easy to work with. Using these models, we can apply powerful genetic methods to learn more quickly all of the possible ways in which these genes and their protein products are controlled and determine how different genes interact with one another. These findings can then be translated to human systems and refined — a dramatic shortcut to gaining important new knowledge and abbreviating the time between gene discovery and the development of therapies targeting the specific changes that lead to cancer.

WHAT WE CAN LEARN FROM THE WORM

What happens when cells "forget" their normal function? Studies of simple organisms such as flies and worms can give us important insights into this question and the development of cancer. For example, researchers studying *C. elegans*, a worm frequently used in genetic studies, observed that certain genetic mutations produced a worm with multiple vulvas. Further study of the mechanisms involved showed that one such mutation was in the worm version of *ras*, an oncogene that is mutated in a variety of human tumors and is thought to play a key role in human carcinogenesis.

The ras mutations in *C. elegans* caused the process of cell differentiation to be disrupted — in effect, the cells on the surface of the worm "forgot" their usual function, were stimulated to undergo too many cell divisions, and formed extra vulvas. This finding provides important clues into the role of the *ras* oncogene during growth and development in both the worm and in humans, and, by demonstrating one manifestation of the effects of a *ras* gene gone awry, could eventually lead to innovative measures that prevent or reverse those effects.



Top: Normal* C. elegans *with a single vulva.
Bottom:* C. elegans *with multiple vulvas due to mutation of the* ras *ongogene.
Photos courtesy of Dr. H. Robert Horvitz, Massachusetts Institute of Technology

Testing new therapeutic and preventive interventions. Cancer therapeutics research will benefit significantly from animal models that faithfully represent the great variety of diseases we call cancer. Developing animal models for human cancer predisposition and development will allow us to test prevention strategies and facilitate the development and evaluation of agents that could intervene in and arrest the disease process. As we approach an era when cancer therapy will be tailored to the particular mutations that promote tumor development, we will need these accurate models to test new therapies more rapidly. These systems will allow us to answer the critical questions of why a particular therapy works in some cancers but not in others. New ideas and new approaches to therapy abound, from manipulation of the immune system to gene therapy; we require experimental settings such as these animal models to emulate quickly and safely the real problems and potentials of 21st century therapeutics.

The Plan

Although the need for this technology and the potential for significant, concrete advances are great, at present we cannot fully exploit this extraordinary opportunity for progress against cancer. Creating mouse and other models of human cancer is now technically possible, but the infrastructure is lacking to develop the range of models necessary to represent human cancer and to make these models available to researchers. The expense and logistics of creating and maintaining these animal models is beyond the budgets available to individual researchers. We need the added investment and infrastructure to support, to help manage, and to coordinate the use of these powerful new preclinical models. Specific steps in our plan include the following:

- We need to support the development of mouse and other non-mammalian models. These preclinical models must be tested and refined to ensure that they accurately reflect important characteristics of human tumors.

PRECLINICAL MODELS RESOURCES

	FY 99
Mouse Models to Study the Biology and Treatment of Human Cancers	**$11.8M**
• Develop programs to improve technology and expertise, and to support, validate, and disseminate models	
• Establish database of all mouse models	
• Conduct pilot projects to validate and improve the usefulness of models	
• Support training of scientists for optimum capability in the use of mouse models	
Non-Mammalian Organism Models to Find Oncogenes, Cancer Pathways, and Screens for Anti-Cancer Drugs	**$6.5M**
• Promote the study of cancer gene homologs in non-mammalian models	
• Develop resources (genetic tools) and centers to aid development of non-mammalian models	
• Establish a multi-organism gene database	
• Support development of screens for anti-cancer drugs in these systems	
Index of All Mouse Cancer-Related Genes — Mouse Tumor Gene Index (TGI)	**$11.0M**
• Produce 50 cDNA libraries from mouse cancer models in one year	
• Produce 100 cDNA libraries from different stages of mouse development and from many organs	
• Use the Human TGI infrastructure to identify 400,000 mouse transcripts for cancer research	
PRECLINICAL MODELS TOTAL	**$29.3M**

- Repositories, distribution mechanisms, and related procedures must be established to make these models available to all researchers.
- The knowledge, expertise, and technology to use these biological models to their fullest potential in cancer research must be fostered.
- A work force must be developed that is expert in the genetic manipulation of mice, the manipulation of other relevant genetic systems, complex genetic analysis, and mouse pathology.

Progress in Pursuit of Our Goals

A Working Group has been convened to delineate the major opportunities and barriers to developing and disseminating biological models for cancer. The group's initial discussions have focused on the issues outlined above and on more precisely defining goals, establishing priorities, and identifying related tasks that must be undertaken to realize goals. Subcommittees of experts in the relevant fields have been established, and we are now engaged in discussions to develop the detailed plans needed to exploit this opportunity.

One of our first tasks, already under way, is to develop a database containing all of the available knowledge about the natural occurrence of tumors in model organisms, particularly the mouse. It will provide baseline information on tumor incidence, type, and outcome for these animals. This information is being collected for the first time and will be an invaluable research resource. The database will be extremely helpful both to investigators needing appropriate animal models for studying tumor development and those seeking to identify the genes that predispose the animals to cancer. This database is one of the first steps in our planning process to expand the use of model organisms in the study of human cancer.

Consequences: Investing versus Waiting

Good biological models quicken the pace of discovery. The use of simple genetic systems has the potential to enhance greatly our understanding of the genetic mechanisms involved in the cancer process and can be expected to uncover new targets for therapeutic and preventive interventions. Past research investments have yielded a wealth of innovative ideas and approaches to early detection, prevention, and treatment of disease. We believe animal models represent the most rapid, efficient, and cost-effective way to assess the potential of these innovations. In all areas of medicine, the new ability to create valid models of specific diseases is revolutionizing safety and efficacy testing of these much needed interventions. Failure to make full use of this breakthrough technology in cancer will greatly limit the number and types of novel therapies that we can test. Moreover, we will continue to be hampered in our ability to priori-

tize promising interventions and assess their readiness for human clinical trials. The backlog of new ideas and new approaches is growing, but we can neither afford nor justify trying them all in humans.

If we fail to enact this plan, we will have abandoned a practical way to test interventions that may allow us to prevent the development and progression of cancer. Without the tools this plan will provide, our understanding of the environmental and dietary factors that alter cancer risk will remain limited.

We are committed to discovering more rapid, more accurate, and more economical means to translate basic research to the benefit of patients, and we believe that animal model technology will increase the flow of ideas into testable clinical applications. If we do not invest in designing new biological models and making them widely available to researchers, we will be tied to a slower pace of progress; too many worthy ideas will have to wait in the long queue for human clinical trials without the guidance compelling results in animals could provide. We must enact this plan to capitalize on this technology's enormous potential to deepen our understanding of cancer and help us find ways to conquer it.

OPPORTUNITY 3
Imaging Technologies

One hundred years ago, Wilhelm Roentgen, a German physicist, demonstrated that x-rays can be used to visualize internal structures of the body. Progressive refinements in technique since then have steadily improved the quality and versatility of the x-ray picture, so that for many decades now, the diagnostic power of the x-ray has pervaded the practice of medicine — the chest film, barium contrast studies of the gastrointestinal tract, and detailed visualization of the coronary arteries are familiar examples. These and other imaging techniques have made it possible to diagnose localized abnormalities, often before they have caused irreversible damage. In no field of medicine has the diagnostic usefulness of the x-ray been more phenomenal than in oncology. In many parts of the body, cancers too small to be detected by physical examination can be pinpointed by imaging and treated before they can spread. This is why x-ray mammography saves the lives of many women diagnosed with early breast cancer.

Over the past quarter century, the entire imaging field has taken a quantum leap forward. Indeed, the practice of diagnostic radiology has been revolutionized, perhaps more dramatically than any other area of clinical medicine. A Rip Van Winkle radiologist, awakening today after a 25-year nap, would be utterly astounded by the sheer richness and precision of the information provided by a routine CT scan of the body. Organs deep within the body can now be biopsied by long, thin needles guided safely to their targets by CT or ultrasound scanning; in many cases, this capability has eliminated the need for general anesthesia and an open surgical procedure. The crude and often painful techniques of the past for visualizing the brain and spinal cord (myelography and pneumoencephalography) have given way to non-invasive, painless, and vastly more informative CT and MRI. Adaptations of MRI permit the refined visualization even of the arteries of major organs without the need for painful and potentially hazardous injection of contrast material into these vessels.

The Goal

Discover and develop techniques that will increase the precision, accuracy, and scope of imaging diagnosis and integrate imaging further into the practice of clinical oncology.

The Opportunity

We already know that several different types of physical processes can interact with living tissue and produce useful images. X-rays can be collected, recorded, and analyzed to produce plain images on film or CT scans. Radioactive material called tracers, when introduced into the body, seek out a particular organ or structure (such as a tumor) and can yield an image of that organ or

structure when the decay of the tracer is detected by special sensing devices. The responses of tissue exposed to a changing magnetic field can be recorded as magnetic resonance images. Sound waves of high frequency (ultrasound) can pass through the body and produce images in real time of rapidly moving or stationary anatomical structures. Yet we still have far to go to realize the full potential even of the techniques already available to us.

Consider just two examples:

First, most routine imaging techniques show us the anatomic size, shape, and in some cases the density of an organ or an abnormality within an organ. Sometimes the appearance of an abnormality is so characteristic that we can infer what the abnormality is (in other words, it strongly suggests a specific diagnosis), but most often it is not.

Certain currently available techniques, such as positron emission tomography (PET) or single photon emission computerized tomography (SPECT) imaging permit visualization of the physiological or metabolic characteristics of a tissue, including tumor tissue. These characteristics might include, for example, the glucose utilization rate or the kinds of receptors covering the surface of the tumor. Such information may soon help us make decisions on how to target particular kinds of therapy to a tumor, or may tell us, without the need for biopsy, how a tumor is responding to a recently administered treatment. Gazing much further into the future, it is even possible to imagine that metabolic imaging techniques eventually may be extended to give information about the disruption of cellular signaling pathways or specific patterns of gene expression.

At the Cutting Edge

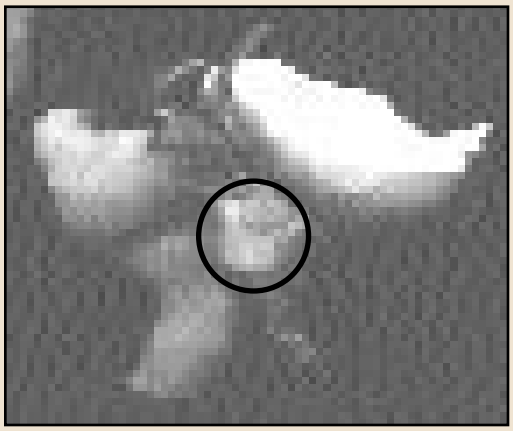
Dress Rehearsals for Surgery: 3-D Prostate Cancer Surgical Rehearsal

X-ray films, CT scans, and MRIs in hand, a prostate surgeon heads down the hall of a hospital. But instead of donning scrubs, entering a surgical suite, and taking scalpel in hand, the surgeon enters a biomedical imaging laboratory, sits down at a computer, and takes mouse in hand. Like an actor rehearsing for the last time before opening night, the surgeon is, through the use of the latest computer technology, rehearsing for the prostatectomy he will perform tomorrow.

Surgery for prostate cancer involves working in an area of a man's anatomy where several delicate organs are housed in close proximity, creating a tough situation for surgeons. More than half of the men who undergo a prostatectomy have surgery-related complications, including impotence and incontinence. But the technology for prostate cancer surgical rehearsal developed by a biomedical imaging resource team at the Mayo Clinic and Foundation, an NCI-designated Comprehensive Cancer Center in Rochester, MN, may provide the key to reducing surgical complications.

Using data from the National Library of Medicine's "Visible Male" from the Visible Human Project, the team of researchers has developed and tested imaging software that enables technicians to combine x-ray, CT scan, and MRI data to create a three-dimensional rendering of the patient's prostate and surrounding organs with the tumor highlighted in bright red. By manipulating the 3-D image, the surgeon can see the relationship of the prostate gland and tumor to the bladder, ureters, seminal vesicles, and other anatomic structures prior to surgery. This information enables the surgeon to determine the best way to conduct the operation.

Testing of surgical rehearsals for prostate cancer patients has begun with a handful of surgeons at the Mayo Clinic, but past success with similar rehearsal techniques for patients undergoing brain surgery gives the researchers hope that once the technology is refined, surgeons will have a powerful tool to help them plan and perform prostatectomies and other surgeries.



Prostate gland with tumor and surrounding structures computed from MRI of a prostate cancer patient. The tumor is highlighted and indicated by a circle.

Photo courtesy of Dr. Richard A. Robb, Mayo Clinic and Foundation.

Second, the application of computer technologies to enhance and manipulate images so that they can be better appreciated by people has been illustrated most dramatically in the pictures beamed back to earth from orbiting satellites or from interplanetary probes. Extensions of this technology have potentially profound implications for analyzing and refining patterns detected in medical images. Neural networks are a component of some artificial intelligence technologies that can be "trained" to recognize patterns. The application of neural networks to patterns imaged using standard x-ray mammography has already suggested that neural networks can be "taught" to distinguish between malignant and non-malignant breast images with impressive accuracy. Since we know that mammography saves lives, the demonstrated potential of these new technologies to enhance mammography has compelling implications for extending image enhancement and pattern recognition to other cancer medicine applications.

Clearly, the richness of possibilities for medical imaging is extensive and wide-ranging. Improved imaging will contribute to a better understanding of human tumor biology, to better means of diagnosis and early detection, and to better prevention and therapy. Paradoxically, this tremendous scientific promise comes at a relatively inhospitable time for the introduction of innovative technologies in medicine. Health care providers are under severe pressure to contain costs and are less willing than in the past to make large capital investments; the promise of more accurate images will not be sufficient to justify new equipment purchases unless there also is evidence that the greater accuracy translates into cost savings or better clinical results. These economic realities are making the industrial developers of imaging technologies reluctant to invest in risky projects that have little or no prospect of near-term gain, even if the potential long-term payoff is very high. Another issue is that device manufacturers are technology oriented and frequently lack expertise in medicine or biology. This means that decisions on what to develop are often made without a strong sense of biomedical priorities.

The Plan

To advance medical imaging technology for the benefit of cancer patients and those at risk, we must address three particularly important challenges. Specifically, we must:

- Develop a plan for a comprehensive imaging research program.
- Coordinate the development of imaging technology with medical need.
- Create a suitable infrastructure for the timely and definitive clinical evaluation of emerging imaging technologies.

In response to these challenges, NCI has created a Working Group devoted to imaging technologies. Identical in concept to the very successful Working Groups devoted to molecular diagnostics and cancer genetics, experts from diverse disciplines have been challenged to help NCI develop a plan for taking full advantage of the current and developing scientific opportunities relating to imaging. The plan will include short, medium, and long-term goals with defined and attainable milestones against which progress can be measured.

In parallel with the Working Group effort, NCI plans to initiate a national forum to bring together biomedical scientists, technology developers, Federal regulators, and health care payer and provider organizations. This forum will provide a catalyst for information exchange and for the formation of partnerships between those who can define the medical needs and those who have the technological expertise to meet them. Inviting the Food and Drug Administration and payer/provider representatives to participate in the process will ensure discussion of issues relating to regulatory and reimbursement decision making. We expect that the ongoing dialogue resulting from this forum will have at least three important outcomes. It will make technology development more relevant to the areas of greatest medical need, help speed the approval of devices, and improve decision making by payers concerning which diagnostic tests should be covered by health care plans.

DIAGNOSTIC IMAGING RESOURCES

	FY99
Metabolic and Physiologic Imaging	**$11.0M**
• Develop functional and physiological imaging techniques for cancer	
Pattern Recognition and Image Enhancement	**$12.0M**
• Develop necessary hardware and software	
Integration of Imaging with Therapy	**$10.0M**
• Develop image-guided therapy	
Clinical Trials	**$3.0M**
• Establish a national network for the rigorous and comprehensive assessment of new imaging techniques	
Training	**$2.0M**
• Establish programs for training the next generation of imaging researchers	
• Develop necessary hardware and software	
Accelerated Technology Transfer	**$1.0M**
• Establish a national forum for information exchange relating to imaging technologies and biomedical need	
DIAGNOSTIC IMAGING TOTAL	**$39.0M**

NCI also plans to establish a national network for evaluating imaging technologies. This cooperative group will include academic centers of excellence and affiliated hospitals in the community with particular expertise in clinical imaging. This group will have two important roles. First, it will work with academic and industrial technology groups to expedite the early clinical testing of promising prototype devices. This will provide the critical information necessary to decide whether innovations are promising and, if so, whether they need improvement before large-scale testing. Second, the group will have the capability to conduct these large-scale, definitive evaluations of imaging innovations, usually comparing the innovation to standard techniques, as soon as such testing is justified by the pilot clinical experience. Evaluations should include measures of diagnostic accuracy, medical benefit, and cost effectiveness compared with widely used standard approaches. NCI anticipates that this cooperative network for assessing new imaging technologies will be well received by commercial technology developers, since it will provide them access to a highly skilled and committed group of clinical investigators for the testing of novel products and approaches. NCI also anticipates significant cost sharing with industry for the support of this activity.

Consequences: Investing versus Waiting

All of these areas are of interest to imaging scientists in academia and industry. If NCI is able to capitalize on the opportunities outlined here, translation of imaging science into clinical reality for people with cancer and those at risk will occur much sooner than is possible at our current level of involvement. The formation of productive consortia between academia and industry will occur much more rapidly if catalyzed by NCI interest and resources. Our participation will ensure the application of emerging technologies to the cancer problem.

Imaging advances will bring earlier and more accurate diagnosis of many cancers, fewer invasive procedures for patients, and a heightened ability to monitor tumor response to treatment. Significant advances in imaging are now possible and will translate directly into larger numbers of lives saved, but their development will be stunted without NCI leadership and investment at this important time.

OPPORTUNITY 4

Defining the Signatures of Cancer Cells: Detection and Diagnosis

In the clinic of the future, Michael, age 65, has arrived for his annual physical examination. After the preliminaries — height, weight, blood pressure — are complete, it's time for some routine blood work. A needle-stick in the finger provides a drop of blood to test for signs of cancer. Sensitive tests look for the presence of tell-tale proteins that might have been secreted from a tumor at a distant site. Most of the results prove negative, but several tests that check for prostate tumor markers show increases in certain circulating proteins since Michael's last exam. A special computer is used to make comparisons with his

past records and with profiles from other men in the same risk groups as Michael. These indicate the need to perform direct tests for prostate cancer, and a biopsy finds a small but potentially dangerous growth of tumor cells. The DNA of these cells is examined and a lightning-quick analysis shows subtle changes in a few genes. A computer is used to connect to a database of DNA samples that can be compared to Michael's DNA. His DNA matches DNA consistent with early-stage prostate cancer that requires immediate treatment; outcome data on individuals with DNA like Michael's suggest his cancer will spread quickly if left untreated. Michael begins treatment soon afterward, and subsequent tests show that the cancer was removed just in time, before it had the chance to spread to distant organs.

Just as each person's signature and fingerprints are distinct from those of every other person, cells likewise have signatures — unique, identifiable characteristics related to their role in the body. During the transformation of a normal cell into a cancer cell, the signature changes, and that change becomes a unique signal of its presence and character. By reading these signals accurately, we will be better able to detect and diagnose individual cancers. Our progress to date in isolating unique identifiers of cancer cells makes this area of research one of extraordinary opportunity for improving patient care.

Detection

It has been shown over and over again that early detection of cancer saves lives. We know that finding tumors when they are smaller and have not spread usually results in a substantially better prognosis for the patient. In short, the earlier a cancer is detected, the better. Accurate early detection methods give us a chance to catch a tumor before it has reached a stage at which effective care is compromised.

Currently, three major approaches are used to detect cancer. The first involves physically detecting the tumor, such as by touch or by x-ray imaging, as in mammography for breast cancer. The second involves recognizing abnormalities caused by the tumor, such as the presence of blood in the stool — a potential sign of colon cancer. The newest method detects molecular changes that only occur in patients with cancer cells. One common use of this method involves checking a blood sample for elevated levels of proteins produced by certain types of tumor cells. One such protein, prostate specific antigen (PSA), is produced by prostate cancer cells. This third area of detection technology provides a wealth of opportunities to develop more sensitive and specific methods for detecting the presence of small tumors, greatly enhancing the chance for curing or controlling cancers.

Diagnosis

The behavior of each cancer — how it responds to therapy, how it changes over time, and whether it threatens the patient — is determined by molecular changes that occur during tumor development. The methods we currently use to diagnose tumors often do not allow us to determine these changes. The problem is one of discrimination. We need to know enough about a particular tumor to make correct choices about therapy and accurate predictions of outcome.

At present, our ability to determine these important tumor traits is too limited. We have achieved significant progress in understanding the molecular basis of cancers, yet our current diagnostic tools do not provide the clarity of information we need for better patient care. For example, two apparently identical breast tumors may have distinct features that caused them to develop differently and will cause them to respond differently to treatment. The inability to identify such crucial characteristics can result in vastly different outcomes for the patient. We must design more sophisticated tools in order to determine the traits of the tumor that dictate treatment choice and predict prognosis.

The Goals

1. Develop new methods for detecting tumors at their earliest stages, when the number of tumor cells is small and the chance for cure or control is greatest.

2. Develop diagnostic tests that will enable us to base treatment choice on the fundamental traits of a tumor that determine the course of its development.

The Opportunities

In the budget proposed by the National Cancer Institute for FY 1997/98, Developmental Diagnostics and Detection Technologies based on the unique signatures of cancer cells were identified as two distinct areas of extraordinary opportunity because of the differing impact they will have on the management of cancer in patients. Subsequent discussions with advisors have made it clear that a unified approach will most rapidly accelerate the discovery process both for new molecular-based detection and diagnostic methods. Therefore, this year we present these opportunities as one, with a cohesive implementation plan to achieve key milestones in both detection and diagnosis.

Detection. Among the exciting new opportunities for major advances in our ability to find cancers in their earliest and most treatable stages is to detect solid tumors by looking for protein molecules secreted only by the tumor cell. The presence of these proteins in body fluids, such as blood, signal cancer. In fact, cancer cells influence the behavior of both neighboring and distant tissues — blood vessels, the kidney, the brain, endocrine glands, and other organs are all subject to changes as tumors grow. We are quickly discovering tumor-secreted proteins that account for these changes, so that developing sensitive methods for detecting them is now feasible.

In addition, subtle but detectable changes in the DNA, cellular proteins, and other molecules in tissue surrounding the site where a tumor was removed may persist if only a few precancerous or cancerous cells remain around the margin. Detecting these changes will enable us to determine with greater confidence whether we have removed the entire tumor. Moreover, periodically monitoring patients for these changes may provide early signals of disease recurrence, or alert us to the existence of residual disease at locations distant from the original tumor site. For all of these reasons, the ability to detect a tumor's molecular signature in body fluids or tissue holds huge potential for catching tumors at their earliest, most controllable stages, and thereby improving the care and prognosis of people with cancer.

Diagnosis. New opportunities now exist for dramatically improving our ability to diagnose and distinguish differences among tumors, leveraging the knowledge we have gained from our investment in the infrastructure for discovery. The first human cancer gene — for retinoblastoma, a rare childhood cancer of the eye — was identified approximately 20 years ago, and progress in identifying all of the genes important in human cancer has been rapid since then. The explosive growth in our knowledge of mechanisms that promote and regulate tumor development is one of the success stories of modern biology. We now understand the molecular basis for many of the changes responsible for tumor development. These advances in our knowledge provide the framework for more precise and complete diagnosis of cancers.

Molecular diagnostics will provide a direct link between the molecular description of cancer cells and patient care. In its simplest terms, this new era in cancer diagnostics will provide a "snapshot" or profile of the tumor's properties at a particular point in time. This snapshot will show the key differences between a normal cell and the cancer cell. Once identified, the abnormal traits of the tumor cell will then be used to plan individual patient care.

Developing a rapid and cost-effective method for taking this snapshot of the tumor cell will be an essential step toward major advances in:

Understanding tumor development by establishing a natural history of tumors for all cancers. A snapshot of cancer cell properties taken at various stages of tumor development will chart the steps of cancer growth. We need to learn the changes that are linked to each stage of tumor development. Does one alteration dictate the alteration that follows? When do the most harmful changes take place?

Classifying tumors into groups based on their fundamental properties. We will then be able to identify tumors that have similar patterns of growth and will respond similarly to various therapies.

Selecting and developing treatment based on molecular changes that occur during tumor development. Diagnostic tests that identify these key molecular

changes will make it possible to make fully informed choices between available therapies and eventually to design new and more effective therapies.

Assessing progress based on a complete picture of the alterations that promote tumor development and a clear indication of the original cancer site. This information will make it possible to predict more accurately the course of disease and will lead to more effective patient care.

The Plan

In the area of *detection,* our plan has three major components:

- We will expand our current knowledge about the proteins secreted by normal and cancer cells to develop new cancer detection tools. Secreted proteins can be recognized, in part, because they carry certain molecular "flags" that denote them as secreted. Using highly sensitive molecular tests, we will catalog proteins secreted by specific tumor cell types. Individual proteins known to be secreted by a particular tumor cell type can then be measured in blood samples. This approach should be applied to all of the common solid tumors — for example, breast, colon, lung, prostate, ovarian, brain, and bladder.

- We will adapt existing gene identification systems, used to find cancer-related genes, to detect extremely small numbers of tumor cells. These methods will enable us to detect accurately and rapidly tumor cells in easily obtained samples of tissue, blood, and/or other body fluids.

- We will design methods of detecting the numerous protein and non-protein molecules made by tumor cells that alter the behavior of both neighboring and distant organs and tissues. Detecting these molecules in tissue would signal the presence of tumor cells in a patient; the tumor cells' location could then be pinpointed by clinical methods.

To increase the usefulness of *diagnostics* in caring for patients, our efforts will be focused on two major areas: developing better diagnostic tests and creating the research structure needed to correlate test results with clinical outcomes. The clear goal of the next generation of diagnostic tests will be to classify tumors into groups that behave and respond in similar ways. As we are better able to see how tumors are alike or different, we will have recognizable targets for which we can select and/or develop effective therapies.

Three approaches will be used:

- We will develop methods for detecting the actual mutations responsible for tumor development in the cell's genes.

- We will develop a picture of key genes that are expressed in the tumor and establish a profile of the proteins found in the tumor. The patterns of gene expression should also indicate the tumor's origin.

- We will identify changes in key communication pathways and other regulatory controls in a tumor cell. Communication or "signaling" pathways are like electrical circuits; they are the mechanisms that cells use to make decisions. In cancer cells, these "circuits" function differently than in normal cells in ways that we can identify and monitor.

The plan for improving cancer diagnosis must include the capacity to evaluate whether the new tests result in better patient outcomes. To develop the research infrastructure needed to do this, we need to support research through which the gene alterations, gene and protein expression levels, and signaling pathway changes underlying the new diagnostic approaches can be established. We will need repositories for tissue and tumor samples provided by patients who wish to participate in this research. The repositories will also store clinical records and will serve as a resource for samples and for comparing prognosis with the various tumor markers measured with the new diagnostic tests. Clinical research will be needed to correlate the tumor profiles with response to different therapies. All of this data must be linked through a network that allows information exchange among all of the researchers and cancer care givers developing and using these new methods.

Progress in Pursuit of Our Goals

In March 1996, the Developmental Diagnostics Working Group was established to provide input on how best to achieve the goals outlined for Developmental Diagnostics in the FY 1997/98 budget request. Its members are outstanding scientists from academia, industry, and government, spanning the cancer research continuum from basic to clinical investigation. The Working Group recommended that NCI support the creation and expansion of technologies to measure genetic changes and establish the patterns of gene and protein expression and function in tumor cells.

The Cancer Genome Anatomy Project (CGAP) will be the principal vehicle for coordinating and achieving advances in molecular detection and diagnostics. The overall goal of CGAP is to determine the complete profile of expressed genes in normal, precancer, and cancer cells, with the aim of making it possible to recognize all major steps of tumor development. We know that cancer is a genetic disease, meaning that mutations in genes are responsible for the development of cancer. But we don't know for every cancer what genes and proteins exist in the normal, the precancerous, and the cancerous cell. Understanding all of the changes cells undergo to reach the malignant state will help us develop new and better diagnostic tools — we will be able to predict the behavior of each particular cancer and design new treatments by knowing exactly what to target to halt the disease process.

The Cancer Genome Anatomy Project has two initial goals. They are:

Establish the *Tumor Gene Index,* a complete index of all expressed genes in cancer cells. This will be done by creating cDNA libraries,

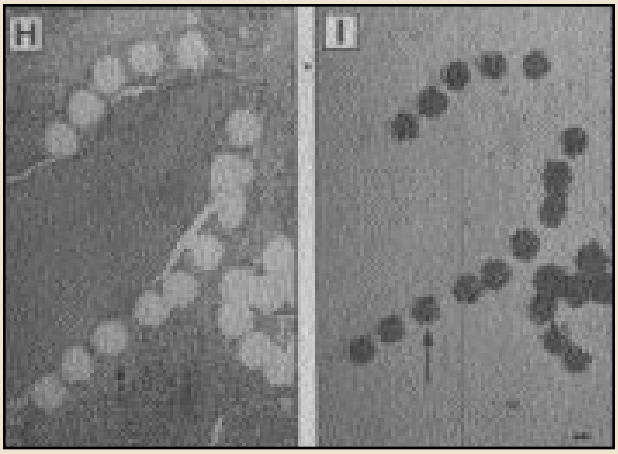
At the Cutting Edge

Laser Capture Microdissection

A scientist looks at tissue through a microscope, focuses on a group of suspect cells, and then pushes a button on the side of the microscope that activates a low-powered laser. The laser passes through a plastic film placed over the tissue and heats it, making it sticky like adhesive tape. The target cells adhere to the plastic, then the plastic is lifted off the slide, removing only the selected cells. The cells' gene and enzyme activity are then immediately analyzed using other research tools to determine if they are precancerous.

The procedure described sounds simple, but as recently as a year ago, scientists who looked at tissue biopsies and spotted cells that appeared to have early signs of cancer had no way to confirm their observations while the tumor was in its earliest and most treatable stages. The tools to extract the cells from the tissue without tedious and inefficient processes did not exist — that is, until a team of researchers from NCI and the NIH's National Center for Research Resources developed a powerful new technique known as Laser Capture Microdissection (LCM), which allows a doctor to extract cells of interest with the simple click of a button.

The possibilities for this new technology are just beginning to take shape. In addition to serving as a technique for detection of precancerous cells, LCM may help record patterns of gene expression in various cell types. It is already being used for the NCI Cancer Genome Anatomy Project's Tumor Gene Index, which seeks, in part, to define patterns of gene expression in normal, precancerous, and malignant cells.



***Using laser capture microdissection, researchers removed cells from a pathological sample of breast cancer* in situ.**
H: pathological sample after tumor cells have been removed by LCM; I: Isolated breast cancer cells attached to transfer film.

Photo courtesy of Dr. Robert Bonner, National Center for Research Resources.

an inventory of synthetic DNA copies of the portions of genes that contain the directions for producing specific proteins. In simple terms, these are the regions that specify the working blueprints of genes. Starting with breast, prostate, lung, colon, and ovarian cancers, researchers will construct libraries of expressed gene sequences. We will gain tremendous scientific insight from comparing cDNA from cancer cells to that from normal cells from the same body site.

Support the development of new technologies that will enable the rapid, accurate analysis of the changes that occur during tumor development.

Sequencing, or deciphering the order of the base pairs of various cancers, is being done in laboratories around the world, but it is a laborious, time-consuming, and expensive process. This is why achieving a complete Tumor Gene Index is so important. As we establish, copy, and index the sequence for each expressed gene in each cancer, we will make it available to the entire scientific community.

The next step will be to use the infrastructure created by the new technologies and the Tumor Gene Index to identify the associations between a tumor's molecular and genetic characteristics and the prognosis of someone who has that tumor.

CGAP will coordinate the efforts of scientists from government, industry, and academia. The research information, infrastructure, and technologies developed through this project will form a springboard for revolutionary approaches to early detection, accurate diagnosis, and appropriate choice of treatment based on more precise molecular knowledge of an individual patient's tumor. What we learn from the CGAP will transform the practice of oncology, expedite research to identify the causes of cancer, and provide targets for the new treatments that we so desperately need.

At the beginning of this section we told you the story of Michael, whose prostate cancer was caught at an early stage by a simple office procedure that was quick, safe, and highly accurate. What we learn through the CGAP will make the characterization of Michael's prostate tumor possible. It will allow us to learn how dangerous his cancer is and how best to treat it. This will become a reality, not just for prostate cancer but for all types of cancer.

Consequences: Investing versus Waiting

We have known for years that certain tumors, such as testicular cancer in men and choriocarcinoma in women, have distinct signature molecules circulating in the blood, and we have been using these characteristic markers to detect and treat disease much earlier than if we had to wait for visible or palpable lumps. We have every reason to believe that all cancers have distinctive signatures that can be used to detect tumors at the earliest possible stage to ensure the best possible outcome for patients. Improved methods for diagnosing tumors are on the horizon. We need to make this vision a reality.

Through this initiative, we have the opportunity to convert our growing knowledge of tumor cell biology into practical advances in patient care. Over time, these advances will transform many aspects of clinical cancer medicine. We will be able to diagnose based on biology, not just on the microscopic appearance of a tumor. By pinpointing the molecular changes that occurred during tumor development, we will be able to predict with accuracy how a tumor will behave and what the patient's outcome will be. We will select therapy based on the tumor's individual biological properties, rather than on empirical guesses. We will uncover new therapeutic targets and make it possible to base clinical trials on tumor characteristics and the patient's cancer risk.

Without national investment, this fundamental transformation of cancer medicine will occur far more slowly, and many lives will be lost unnecessarily. A portion of the work necessary to effect these developments would proceed in academia and industry, but less rapidly and with less intensity and coordination. Certain necessary steps may not occur at all; it is unlikely that the essential research infrastructure to support a cancer detection and diagnostics effort of this type (tissue banks and the information links between banks,

Signatures of Cancer Cells

	FY 99
DETECTION:	
Identify Proteins Secreted from Tumor Cells	**$9.5M**
• Prepare full length cDNA libraries and perform 5' sequencing (500,000 reads/year)	
• Test candidate secreted proteins (200 proteins/10 tumor types)	
• Test candidate antibodies for each tumor type (10 grants/year)	
Develop Sensitive Assays for Secreted Proteins	**$5.0M**
• Development of high-throughput and sensitive assays for protein detection in blood samples (10 grants/year)	
Tumor Cell Detection	**$2.0M**
• Promote research for technologies to detect tumor cells in bodily fluids and other easily sampled areas (10 grants/year)	
DIAGNOSIS:	
Tumor Gene Index (TGI)	**$18.5M**
• Clone and sequence 1,000,000 additional human ESTs.	
• Tag 50,000 clones at 5' end to provide protein encoding sequences for new genes	
• Develop human cDNA libraries with high proportion of full-length transcripts	
• Sequence full transcripts of 20,000 genes identified in TGI	
• Map 20,000 cDNAs from TGI using radiation hybrid panels	
• Develop vector systems to shuttle cDNA libraries into various expression systems, including yeast two-hybrid	
• Start development of high-resolution gene-based map of human genome — sequence tag 12,000 genes in eight individuals	
Mutation Detection	**$9.5M**
• Establish patterns of genetic changes that accompany tumor development	
• Establish five centers to test candidate genes and measure mutations	
Expression Detection	**$10.5M**
• Establish five centers for expression detection — capture data on informatics system	
• Make widely available new high-throughput detection technologies	
Pathway Detection	**$1.7M**
• Determine active pathways in various tumors by testing panels of antibodies against phosphorylation sites	
Clinical Trials	**$6.8M**
• Establish database and tumor registries of known outcomes	
DETECTION AND DIAGNOSIS TOTAL	**$63.5M**

tumor registries, and the clinical trials program) can be organized and supported by another means.

Without this investment, cancer treatment choices will continue to be based on unsatisfactory and incomplete methods of diagnosis. We will not be able to separate tumors into classes based on their molecular differences. Since these differences are the reasons that tumors behave and respond differently, our insights into treatment choice and outcome will continue to be blurred. Progress will not be stopped, but an important opportunity for real advancement will be missed.

NCI's Challenge

We cannot conquer what we will not fight. We have founded our fight against cancer in the power and process of science and have enlisted the best scientists and clinicians to create the knowledge and the tools we need to succeed. But will we?

Knowledge about the fundamental nature of cancer is exploding. Technology is giving us new instruments with which to see and understand cancer much as the Hubble telescope has given us a new eye on the universe itself. Investments made to achieve our accumulated knowledge and technical capacity are beginning to pay off — cancer mortality rates overall, and rates for many individual cancers, are finally falling, though not as quickly as we would like. And one thing is clear: these successes have resulted from the application of research — research on how lifestyle and environment affect cancer risk, on ways to prevent and detect cancers more readily, and on how to treat cancers more effectively.

Without doubt, we are in a golden age of discovery, one unique in human history. The NCI has engaged the best minds from diverse disciplines to assess how best to foster discovery, facilitate its application to the care of people with cancer and those at risk, and topple barriers to progress. Throughout these intense deliberations, all of us who are dedicated to the fight against cancer returned to this central question: "What more must we do to convert this golden age of discovery to the golden age in the prevention and cure of cancer we have so steadfastly sought?"

Research into the causes of cancer is our only route to effective prevention. Research into detection techniques is enhancing traditionally successful therapy by enabling us to detect cancers at their earliest, most curable stages. Research into the life and death of cancer cells is leading to incremental success in curative therapy. Our successes have shown us that no one approach will conquer the many different diseases we call cancer. We know progress can be made, and we know it will have its roots in discovery. But it is clear that the gap that still exists between discovery and application will not be closed unless we now set in place structures that will speed the engine of discovery, create bridges between all components of the cancer research enterprise, and encompass the care of those with cancer and those at risk into our national research system.

At the beginning of this budget document, we described three interconnected classes of research: laboratory, clinic, and population. While this budget is designed to assure that each thrives, we believe firmly that timely movement towards cancer cure and prevention will happen only when the current gap between discovery and application is spanned. To do this, we must create a system of bridges — among all aspects of research, between research and clinical practice, between research and industry, and between the cancer research enterprise and the American people. We must nurture and strengthen the ties among these diverse research areas, and between the research enterprise and those whose lives cancer touches, to ensure that the benefits reaped by our new ideas and new technologies flow directly into the reduction of suffering from cancer.

In this final section of NCI's budget, we present our plan to meet the challenge of building those bridges that will eventually conquer cancer.

The Challenge and the Plan

The challenge before us is immense. How will we convert our knowledge of cancer into advances in prevention and care on the scale that is needed to conquer cancer? We must enter a new era — one in which scientific knowledge, rather than empiricism, directs our efforts in the fight against cancer. As laboratory, clinical, and population research reveals ever more about the inner workings of cells and the ways in which people and cancer cells behave, the challenge before us is to convert this knowledge quickly into practical, affordable, and effective interventions that restore cancer patients to health or prevent the development of these diseases in all segments of our population.

To meet this challenge, we must have a clinical research base that can bring the best of our developing knowledge — the best ideas, technologies, and people — to the problems of cancer prevention and care. The dismaying fact that only about two percent of adult cancer patients participate in any type of clinical trial means that answers come slowly, and large numbers of patients do not have access to the latest developments. To accelerate our ability to find answers to crucial clinical questions, we must dramatically increase access to and participation in clinical trials. We must supply the structures and mechanisms that will not just span the gap between discovery and application but will transform the process by which we bring discoveries to the benefit of people and allow us to conquer all types of cancer.

The response to this challenge requires increased investment in seven key areas listed below.

NCI Challenge

(dollars in millions)

Additional Increases Beyond Core and Investment Requests

		FY 1999
1.	National Clinical Trials Program	$170.0
2.	Investigator-Initiated Research	40.4
3.	Support for Clinical Investigators	66.0
4.	Cancer Centers: Restructuring and Expansion	70.0
5.	Cancer Informatics and Information Flow	20.0
6.	Studying Emerging Trends in Cancer	25.0
7.	Training and Education	34.1
	TOTAL ADDITIONAL INCREASE FOR THE NCI CHALLENGE	**$425.5**

National Clinical Trials Program

The importance of a strong clinical trials program — and our urgent need to expand the Nation's current clinical trials infrastructure — cannot be overstated. Clinical trials are the crucial final steps in the process of developing new cancer treatments, preventive measures, and detection and diagnostic techniques. As the place where promising new strategies from the laboratory bench are applied for the first time to real human problems at the bedside, clinical trials represent the best opportunity for patients to receive state-of-the-art care while adding greatly to our understanding of cancer and helping to create tomorrow's interventions.

Why, then, do so few people — only about two percent of adult cancer patients — participate in clinical trials? The barriers to participation, some of which are discussed below, are not insurmountable. But we need a robust clinical trials infrastructure to speed the way. We need to ensure that *every* American who wishes to participate in a clinical trial is able to do so. In short, we need to break down the barriers to clinical trial participation for patients, their families, at-risk individuals, and physicians.

Initially, we are aiming for a five fold increase over the next five years in the number of people participating in cancer prevention, detection, diagnosis, and treatment trials through the NCI-supported Cooperative Treatment Trials Program. Currently, approximately 300,000 individuals participate in treatment clinical trials; increasing this number fivefold will ensure that over one million patients each year will have access to the latest treatments and preventive, detection, and diagnostic techniques through a clinical trial.

An expanded and strengthened clinical trials program will challenge us in other areas, as well:

Prevention and early detection. As we are able to identify more individuals who are at risk, whether because of their genetic profile, their environment, or other factors, we need trials of drugs, dietary interventions, and new technologies to prevent their cancer, or to catch it early, before it has had time to spread.

Diagnosis. New, minimally invasive diagnostic techniques emerging from the work of the NCI's Cancer Genome Anatomy Project and elsewhere must also be tested in people.

Treatment. For most types of cancer, current treatments are inadequate. New and highly promising strategies for cancer treatment are emerging through our ever increasing understanding of basic biology; we must speed their development by testing them in people as rapidly and efficiently as possible.

A serious barrier to progress is the growing reluctance of health care payers and providers, particularly managed care organizations, to pay even the routine clinical care costs of patients participating in early clinical trials, thus limiting patients' access to research studies. But treatment and prevention advances must not be sacrificed to the cost consciousness now driving the health care industry. Therefore, the NCI is actively negotiating with representatives of the industry to arrive at mutually agreeable solutions. NCI maintains that it is the legitimate responsibility of the insurance industry to reimburse the costs of routine medical care of cancer patients in all phases of high-quality research trials. For certain innovative trials in which patient care costs are significantly higher than routine care for the same condition, it may be appropriate to consider cost sharing between the insurer and the research sponsor. However, regardless of the cost, for certain people with otherwise untreatable or incurable cancers, a clinical trial may represent the best available treatment.

New Therapeutic and Preventive Agents for Cancer. Our clinical trials system not only allows us to refine current therapies but provides the mechanism to rapidly test new ideas. The explosion of biological discovery presents us with an additional challenge for the development of new therapeutic and preventive agents for cancer. As academia and industry have begun to realize the potential for the discovery of cancer therapeutics inherent in biology, chemistry, and engineering, the number of discoveries that are worth developing into therapeutics or preventives exceeds the current capacity of the biomedical research community. Academic investigators do not themselves have the resources for animal testing of new compounds that they discover, nor the resources for

the scale-up synthesis and detailed pharmacology, formulation, and animal toxicology that must precede clinical testing in people. These functions are ordinarily performed by drug or biotechnology companies, but the willingness of a company to assume these costs depends on many factors other than the inherent promise of the discovery itself. NCI's long experience with cancer drug development will enable us to expedite significantly the flow of discoveries from laboratory to clinic.

We propose, therefore, a significant expansion of NCI's preclinical development capacity. Our goal is to begin clinical trials with 20 promising new agents. NCI will solicit proposals from the research community and will select the most promising development candidates via a competitive process. NCI will then commit to developing these particularly promising drug candidates to enable their testing in the clinic.

Budget for the National Clinical Trials Program

We request $170 million for the National Clinical Trials Program in FY 1999. These funds will enable us to:

- Include $30 million in the Research Project Grant pool to support investigator-initiated clinical trials.
- Provide $60 million to the Clinical Cooperative Groups to cover research costs for an additional 20,000 patients.
- Provide $40 million for cancer prevention trials, primarily through NCI's extramural program. We anticipate targeting 20,000 individuals per site for prostate, breast, colon, and lung cancer prevention trials over four years (80,000 total).
- Use $20 million for clinical trials conducted by the NCI Intramural Program.
- Devote $20 million to enhance the national capacity to get discoveries translated into new drugs and into the clinic for initial testing in people

Total for the National Clinical Trials Program: $170 Million

Investigator-Initiated Research

An enhanced level of support for all types of investigator-initiated research remains a fundamental need. Research in the laboratory, clinic, and community provides the platform on which translational research and clinical testing stand. In basic investigation, we now need to complete the picture of how the cell works and how its molecular circuits go awry in cancer. This is an enormous undertaking, but it is the foundation of future medicine — the pivotal base from which we will create the interventions that translate our knowledge into real improvement in cancer prevention and care.

We also need to make important additions to our research portfolios in areas that will support the crucial process of translation — the generation of clinical hypotheses from basic information and the testing of these hypotheses in applications for people.

Today, NCI can only support approximately the top 25 percent of the grants in the Research Project Grant pool. To ensure that excellent ideas have the chance to be tested, and new investigators are attracted to research on cancer, we need to fund the top 40 percent.

Sometimes, however, important research flows not from the laboratory of an individual investigator but from the collaboration between two or more cancer centers or other scientific organizations. Collaborative efforts are particularly important to the development of new cancer treatments and preventive agents. The NCI supports such collaborations in part through its Program Project Grant (see page 32) and Cooperative Agreement mechanisms. To encourage and facilitate multidisciplinary collaborations, we wish to double the number of competing Program Project grants and Collaborative Agreements.

Budget for Investigator-Initiated Research

We are requesting $40.4 million beyond the core budget and Extraordinary Opportunities for Investigator-Initiated Research in FY 1999. These funds will enable us to:

- Fund approximately 1,500 new and competing renewal research project grants at peer-reviewed approved recommended levels, at an average cost of $325 thousand.
- Fund the top 40 percent of single investigator grants.
- Double the number of competing Program Project grants and collaborative agreements. Fund more translational research projects.

Total Additional Funding for Investigator-Initiated Research:
$40.4 Million

Support for Clinical Investigators

In recent years, changes in the organization and financing of health care have resulted in significantly decreased revenues at many academic health centers. The resulting economic pressures have adversely affected clinical investigators — and, potentially, their research — in those centers; in particular, today's investigator frequently finds protected time for research to be an exceedingly hard commodity to secure. Unless clinical investigators receive the support they need to carry out research, many of the high-quality treatment, detection, diagnosis, and prevention studies that we desperately need will be delayed or even dropped.

Therefore, we must create and maintain an environment that supports and encourages health care professionals who are involved in clinical research. We propose to do this by providing partial salary expenses for "protected" research time for 10 to 15 investigators at most of the 57 NCI-designated Cancer Centers. Clinical investigators involved in prevention and control research through Community Clinical Oncology Programs will also receive partial salary support. In addition, we must support training for health care professionals at any stage of their career who wish to become involved in clinical research.

This is a difficult charge in a dynamic and rapidly changing health care environment, but we cannot hope to succeed in meeting our challenge without a sufficient workforce of investigators appropriately trained to bring our discoveries to the benefit of patients.

Budget for Support for Clinical Investigators

We are requesting $66 million to support clinical investigators in FY 1999. These funds will enable us to:

- Use $60 million for partial salary support for 10 to 15 investigators at most NCI-designated Cancer Centers. The first year, approximately 600 investigators will be supported at $75 thousand to $100 thousand per year; this number will increase to approximately 800 investigators by 2001.
- Use $6 million for partial salary support for approximately 75 investigators in prevention and control research through the Community Clinical Oncology Program and through investigator-initiated research at $75 thousand to $100 thousand per year.

Total Support for Clinical Investigators:
$66.0 Million

Cancer Centers: Restructuring and Expansion

There are currently about 70 research centers nationwide that have the critical mass of NCI-supported research to benefit from core support under the NCI Cancer Centers grant mechanism. Of these, NCI awards cancer center support grants to 57. We believe that this program should grow over the next few years to include all institutions for which this program could be significantly beneficial. Therefore, we wish to expand the Cancer Centers Program to include 60 Centers in FY 1999, 65 in FY 2000, and 70 in FY 2001. Such an increase will increase geographical distribution of Centers and increase the versatility of the Centers program as an agent of discovery.

Budget for Cancer Centers: Restructuring and Expansion

We are requesting $70 million for this area for FY 1999. These funds will enable:

- $30 million to be used to expand existing core-supported NCI sponsored Centers.
- $7.5 million will be used to develop five new Cancer Centers.
- $2.5 million to be used to help five additional institutions begin the process of qualifying for designation as an NCI Cancer Center.
- $30 million to permit the doubling of the funding for Specialized Programs of Research Excellence (SPOREs -- see p. 36) program.

Total for Cancer Centers Restructuring and Expansion:
$70.0 Million

Informatics and Information Flow

The power of computer-based communications and the capabilities of the World Wide Web will make possible unprecedented levels of research cooperation. Slow and cumbersome paper-based systems of data collection for multi-center studies will give way to electronic communication, facilitated by enhanced links between sites of care delivery (hospitals, offices, and clinics) and the research databases of investigators. Currently, however, incompatible informatics systems are in use throughout NCI's clinical trials program. Because of this, the planning and execution of large scale studies with multiple cooperative groups are labor-intensive and time-consuming. We need to institute state-of-the-art informatics systems for clinical trials that promote full compatibility among all participants in the program.

To address the opportunities and challenges presented by the revolution in electronic communications, NCI is now planning a new architecture for the flow of information in its clinical trials programs — a Cancer Informatics Infrastructure (CII). In collaboration with other Federal agencies, and with the participation of many external scientists and clinicians, NCI is developing the CII to expedite the conduct of all types of intervention studies — prevention, diagnosis, and treatment. NCI is modernizing information links with its investigators in a manner that will be compatible with standards set by the international committee now studying this issue for North America, Europe, and Japan. We are also revising our criteria and standards for reporting adverse events. The result will be common terminology and reporting requirements that will greatly increase the speed, efficiency, and accuracy of results reporting.

The twin goals of the CII are to lower the barriers for patients, families, at-risk individuals, and physicians to learn about available clinical trials, and to create an infrastructure that facilitates information exchange among researchers, clinicians, and the public. The CII will greatly enhance NCI's current activities to provide the general public with up-to-date information about new research results, available clinical trials in

diagnosis, treatment, and prevention, and contact points for additional information. For example, instructional modules on computers, tailored to individual needs, can supplement current standard techniques for teaching people about difficult concepts like the risk of getting a disease given a certain genetic predisposition. When housed in kiosks in public places like libraries or malls, computers can inform the public about research results or studies of personal interest and relevance. Such kiosks could also be an effective way to reach people in underserved areas. NCI is already exploring this possibility in collaboration with the library system in the state of Maryland. With the active participation of several patient advocate groups, NCI is engaged in an effort to create a "patient friendly" version of PDQ, the NCI's comprehensive cancer information database, containing information in non-technical language on cancer and on opportunities for participating in investigational studies of new approaches to prevention, diagnosis, and treatment.

Budget for Cancer Informatics and Information Flow

We are requesting $20 million to facilitate this effort. These funds will:

- Support multicenter clinical trials activity, as well as development of expert systems, data collection, and analysis systems.
- Ensure widespread availability of cancer information for patients and their families.
- These efforts will be supported through the Clinical Cooperative Groups Program and the Cancer Prevention and Control activities.

Total for Cancer Informatics and Information Flow:
$20.0 Million

Studying Emerging Trends

Monitoring emerging trends in cancer incidence, survival, and death among populations — changes in our national cancer burden — and the factors that influence these measures, is extremely important. The NCI's primary means of studying such trends is the Surveillance, Epidemiology, and End Results (SEER) database, which tracks the impact of cancer on the general population. For over 20 years, SEER has allowed us to identify environmental carcinogens, to track the cancer-related effects of tobacco on men and women, to identify geographic areas with higher than average rates of cancer, to study patterns and outcomes of cancer care, and to identify risk groups for research and public health intervention programs, all while maintaining the highest level of confidentiality and privacy.

SEER should be not only a means of understanding the past but serve as a window into the future. We want to ensure that SEER and related health information systems not only accurately track changes in cancer rates, but also contain information that will enhance researchers' ability to generate hypotheses and interpret observed changes in trends over time.

Developing and linking databases containing different kinds of health-related information on populations can provide a very powerful tool for analyzing factors (risk factors, screening, treatment, and health practices) that influence cancer rates, planning and evaluating population-based prevention and control interventions, and conducting other special analyses. For example, linkages between SEER and the comprehensive Medicare administrative database are already providing valuable information on relationships between health care resource utilization, costs, and medical outcome. The Breast Cancer Surveillance Consortium, an enhanced information system created to monitor the accuracy and performance of mammography screening in community practice, has led to the development of data linkages among radiologic practices, pathology laboratories, and cancer registries to obtain data on the spectrum of care from screening through treatment. We need to extend these specialized surveillance efforts to

include information on other cancer sites and on underserved and special populations.

Advances in information technology will enable linkages like these to be established much more easily than in the past and in time will facilitate the creation of databases through electronic transfer of information from electronic source documents. As always, procedures and policies will be needed to ensure individual privacy and confidentiality as these new systems develop.

Budget for Studying Emerging Trends

Funds are requested to facilitate the study of emerging trends in cancer.

- $5 million will be used to enhance the Breast Cancer Surveillance Consortium, collecting more complete data on risk factors for breast cancer incidence, prognosis, and quality of life.
- $6 million will support development of a population-based Colorectal Cancer Surveillance Health Information System.
- $5 million will be used to conduct surveillance research on the utility of new database linkages (for example, with other Federal agencies and private-sector organizations).
- $3 million will support infrastructure systems for managing confidential health data, employing information technology advances.
- $2.5 million will expand SEER special studies on patterns of care for diagnosis and treatment, risk factors, and screening and treatment in community practice.
- $2 million will be used to adapt geographic information systems for cancer surveillance, particularly concerning the impact of sociodemographic and environmental factors.
- $1.5 million will enable us to expand methodologic and modeling research related to cancer surveillance.

Total Budget for Studying Emerging Trends: $25.0 Million

Training and Education

We have been emphasizing the importance of new individuals who will be the leaders in accomplishing the complex tasks of translating discoveries into interventions. We need new kinds of scientists who can cross disciplinary boundaries. Where will they come from?

We must take steps now to ensure that some of the brightest, most creative young people from every segment of the American population enter the cancer research field. We must convince some of them that the field of translational research offers tremendous challenges and rewards. Moreover, we need to persuade individuals from untapped segments of the research community to change direction and join us in these translational efforts. This kind of research is often conducted by physician-scientists and other investigators who possess a broad base of knowledge and expertise in basic science, epidemiology, clinical oncology, and clinical investigation. The training of such individuals takes many years. Despite the scientific and medical rewards of careers in this area, there are also substantial disincentives.

We must also put into place initiatives for us to cross-train researchers within a variety of disciplines.

Finally, it is time for us to focus additional attention on the needs of minority students and young scientists and to make these needs a major thrust of NCI's training activities. Current NCI minority initiatives have shown some success in broadening training opportunities for minority scientists, but more efforts are needed. We must find ways to attract more minority students into biomedical science and more minority biomedical trainees into cancer research. Successful efforts to do this will need to be ambitiously conceived and will need to start early in the educational process. Enhancement of NCI's training programs for minority trainees is needed in order to provide promising young scientists access to high-quality training opportunities in outstanding laboratories and clinics across the entire biomedical spectrum.

Budget for Training and Education

We are requesting $34.1 million in FY 1999 to facilitate training and education.

- $10 million will be used for education and training awards to individuals and institutions. Awards will range from $22 thousand to $30 thousand and will be given to 300 to 350 trainees, a portion of which will be pre-doctoral.

- $5 million will be used to award 20 to 25 NCI Research Career Awards ("K" Awards), of which $1.0 million will be targeted for awards to minority students.

- $2.1 million will be used to support intramural research training programs (for example, the NCI Scholars Program), of which $1.1 million will be targeted for minority populations.

- $3 million will be used to augment the Cancer Education Program (R-25) to further the cancer education curriculum and student development in cancer research.

- $4 million will be used to train 30 to 50 individuals in prevention-related research, using both in-house and grant mechanisms.

- $3 million will be used to double the current number of investigators supported through Temin Awards. This will increase the number of recipients of this prestigious award by 20 to 25 scientists.

- $7 million will be used to provide additional training support through Research Project Grant awards, which includes approximately $4.0 million for minority-targeted programs.

Total for Training and Education:
$34.1 Million

National Cancer Institute 1999 Bypass Budget Request

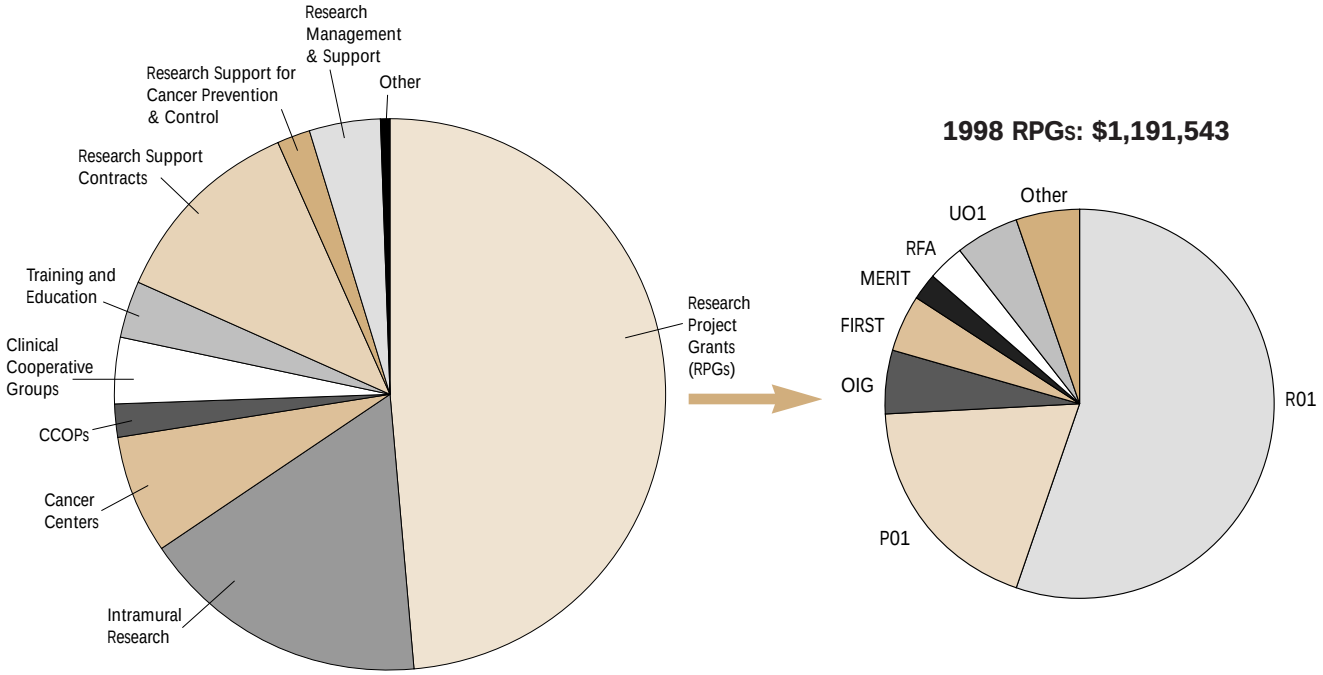
(dollars in thousands)

	1996 Actuals	1997 Operating Level	1998 President's Budget	1999 Bypass Budget
Research Project Grants (RPGs):				
Ongoing	$752,683	$829,722	$877,624	$909,023
New (New and Renewal)	267,062	264,942	266,520	281,794
Small Business Innovation Research	35,643	45,952	47,399	49,058
Subtotal	1,055,388	1,140,616	1,191,543	1,239,875
Intramural Research*	406,891	415,816	412,805	434,253
Cancer Centers	163,391	167,179	171,135	184,173
Clinical Trials Infrastructure:				
Clinical Cooperative Groups	89,244	88,462	92,960	101,214
CCOPs	37,963	46,574	47,163	49,314
Subtotal	127,207	135,036	140,123	150,528
Training and Education	71,267	80,465	78,955	87,339
Research Support Contracts*	276,486	285,230	289,991	307,627
Cancer Control Management & Support	44,877	55,664	47,321	50,659
Research Management & Support	100,831	99,957	100,793	108,820
Other**	8,602	9,102	9,072	16,726
TOTAL	**$2,254,940**	**$2,389,065**	**$2,441,738**	**$2,580,000**
Cancer Control included above	*$216,187*	*$231,708*	*$240,348*	*$263,601*
Additional Increases				
Extraordinary Opportunities				185,500
NCI Challenge				425,500
TOTAL Bypass Budget				**$3,191,000**

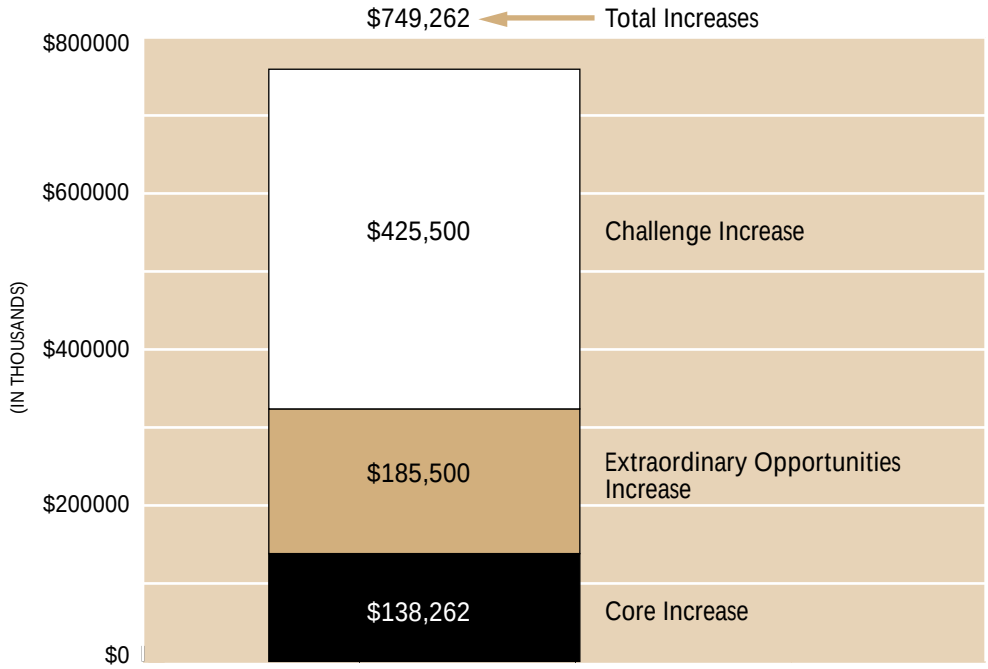
1999 Bypass Budget

(dollars in thousands)

Mechanism Allocation
1998 President's Budget
$2,441,738



1999 Bypass Budget Proposed Increases



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NATIONAL CANCER INSTITUTE

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