When I look into the eyes of a patient losing the battle with cancer, I say to myself, "It doesn't have to be this way."

— Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute,
physician, cancer survivor

The Nation's Investment in Cancer Research

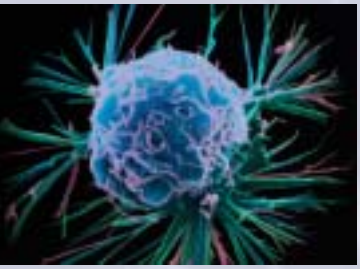
A Plan and Budget Proposal for Fiscal Year 2004

Prepared by the Director National Cancer Institute

NATIONAL INSTITUTES OF HEALTH
U.S. Department of Health and Human Services

The National Cancer Institute

. . . working to achieve a future when all cancers are controlled or eliminated.



Through studies of the **cell**, we:

- Explore how specific cancer-causing mutations and protein errors disrupt normal cellular communication and lead to uncontrolled growth and loss of normal function.
- Learn which genes and proteins play a key role in cancer invasion and spread.
- Develop molecular agents that will interact with malfunctioning proteins to prevent cancerous growth.

With studies of cancer in the context of the **person**, we:

- Identify the integral ways that surrounding cells and tissues contribute to tumor growth — and the means of manipulating this microenvironment to defeat the cancer.
- Apply new technologies and informatics to detect cancer and monitor therapy.
- Learn how to prevent and treat cancer with agents and technologies that attack the cancer, but leave the person unharmed.

With **population** studies, we:

- Investigate gene-environment interactions that increase people's risk of developing cancer and their need for enhancing prevention and early detection measures.
- Identify specific ways to reduce cancer risk by changing behavior and eliminating harmful environmental exposures.
- Develop effective communication and delivery strategies to ensure that all people benefit from cancer prevention, early detection, and treatment.

"Without research, there is no hope."

— The Honorable Paul G. Rogers,
Sponsor, National Cancer Act of 1971

Front cover graphic: Scanning electron micrograph of metastatic lung cancer cells in culture, courtesy of Jeffrey Wyckoff, Jeffrey E. Segall, and John Condeelis at the Albert Einstein College of Medicine and the Analytical Imaging Facility at the Albert Einstein College of Medicine, an Albert Einstein Comprehensive Cancer Center shared resource.

Director's Message

We as a nation stand at that defining moment in history when a surge of new technologies and the fruits of many years of investigation will yield, over the next two decades, unimagined leaps forward in our understanding of cancer and our ability to control and eliminate it. To take full advantage of these opportunities, three themes will dominate NCI's planning and decision making: discovery, development, and delivery. Our challenge will be to continue to accelerate the engine of **discovery**; to translate knowledge gained about the genetic, molecular, and cellular basis of cancer into the **development** of interventions to detect, diagnose, treat, and prevent cancer; and to ensure that these interventions are **delivered** to all who need them.

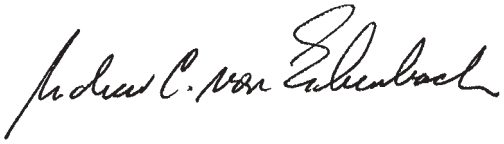
We need to *hone our efforts toward an integrated systems approach to the study of cancer*. We must take advantage of the explosion in technology and biological research to comprehensively weave together the disparate pieces of knowledge that reveal how cancer develops and progresses within the context of the human system. That is, we must consider the protein along with the gene that produces it, the tumor in the context of both its immediate "microenvironment" and the broader environment of the body, and the whole person in the context of the behavioral, social, and environmental factors that influence cancer.

We must *ensure the application of our research knowledge to cancer care*. NCI will collaborate with other agencies and private groups to eliminate unnecessary delays, along the pathway of discovery-development-delivery for lifesaving interventions against cancer. While adhering to our NCI mandate, I am committing NCI to rigorously disseminate our research results, with special emphasis on our comprehensive Cancer Centers, to inform both clinical practice and public health with state-of-the-art science.

For Fiscal Year 2004, we are *adding to our plan and budget proposal new initiatives* to better understand the tumor microenvironment, cancer survivorship, and the interface of aging and cancer. We also place greater emphasis on translational research to move potential preventive, diagnostic, and therapeutic interventions into clinical trials and to integrate more effective cancer care and control interventions into clinical practice and public health programs. Our intramural research program will set a new standard for exemplary translational research. We are *working to find new and more effective ways to collaborate aggressively* both inside and outside of the National Institutes of Health, especially through partnerships with our Nation's community of scientists, physicians, nurses, cancer survivors, and other advocates.

We *will redouble our efforts to eliminate disparities* by ensuring that every American, regardless of race, income, and gender, has access to high quality and timely cancer prevention, screening, diagnosis, and treatment. And we will strive to understand and reduce biologic, socioeconomic, and cultural disparities in the incidence of cancer among diverse population groups.

We will also ask that our programs be examined against the criteria recently established in support of the President's Management Agenda, and I am *committed to making sure that progress toward the goals described in the following pages is evaluated* against the objectives of sound and comprehensive science.



Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute
October 2002

Table of Contents

Executive Summary

The goal of the National Cancer Institute is to achieve a future when all cancers are controlled or eliminated, by stimulating and supporting research and its application. We provide vision and leadership to the cancer community as we strive to more fully integrate **discovery** activities through interdisciplinary collaborations, to accelerate the **development** of interventions and new technology through translational research, and to ensure the **delivery** of these interventions through clinical and public health programs.

Recent reports indicate that overall cancer death rates decreased from 1993 to 1999, while rates of cancer incidence stabilized over a similar timeframe. More people are getting screened for breast, cervical, and colorectal cancers, and more practitioners are adopting state-of-the-art cancer treatments. But we still need to employ greater efforts to reduce tobacco use, weight gain, and sun exposure and to increase physical activity. We also need to reduce rates of some cancers that are still on the rise. These include non-Hodgkin's lymphoma, melanoma, cancers of the liver and esophagus, as well as breast and lung cancer in women.

Trends in various population groups differ substantially by cancer site, sex, and race, and we must redouble our efforts to eliminate persistent cancer-related health disparities. Because of the increasing size of the population and the growing proportion of older persons, researchers expect the cancer burden in the United States to increase substantially over the next several decades. Our changing age structure will require aggressive strategies for cancer prevention and early detection, social support, treatment and medical care, clinical trial design and enrollment, research, and surveillance. In addition, access to supportive, palliative, and general medical services must be optimized.

The framework for the NCI budget is built on priorities that are broadly applicable to cancer research and development and our ability to prevent, control, detect and quickly diagnose, treat, and care for patients with all types of cancer. Within that framework, NCI also carries out an extensive program to develop **National Agendas for Disease-Specific Research**, charting the course primarily through advice from experts in Progress Review Groups (PRGs). We address PRG recommendations by modifying and supplementing existing research programs, encouraging scientists to apply for disease-specific research funding, and developing new initiatives when needed. NCI supports research focused on specific types of cancer through broad-based initiatives such as the Specialized Programs of Research Excellence, the Early Detection Research Network, the Innovative Molecular Analysis Technologies Program, and the Mouse Models of Human Cancers Consortium. Funding for disease-specific research is an integral part of many NCI initiatives.

Our total proposed Fiscal Year 2004 Budget Request is $5,986,000,000. This represents an increase of $1,348,131,000 over the Fiscal Year 2003 President's Budget. Of this increase, $294,014,000 will be provided to continue NCI commitments into 2004 (Core Budget). An additional $577,517,000 will be used for **Building the Nation's Cancer Research Capacity**, $266,250,000 will support **Advancing Discovery and Its Application**, and $210,350,000 will fund research for **Addressing Areas of Public Health Emphasis**. While we are not requesting increases in funding for Cancer Research Training and Career Development or for Studying Emerging Trends, these continue to be priorities for NCI.

Building the Nation's Cancer Research Capacity

Bringing the benefits of cancer research to the American people depends on building and sustaining the strong research mechanisms, support structures, and collaborations that enable us to pursue

rapidly evolving discoveries. NCI must provide the vision, creative environment, and diverse resources needed to ensure a fast paced and synergistic flow of innovative thinking among scientists in disparate scientific disciplines. We must also leverage our collaborations with other government agencies, academia, and industry, focused on steering major breakthroughs toward the delivery of effective cancer interventions.

Investigator-Initiated Research has always been the driving force behind advances in biomedical research. Access to powerful new tools, special resources, and scientific collaborations are increasingly important to an investigator's ability to develop the independent concepts that lead to discovery and translate results to targeted drugs and treatment. NCI aims to balance the flow of resources to ensure that the best ideas are promoted through flexible funding options such as cooperative agreements, seed funds, and supplemental funds for unanticipated opportunities. Compelling proposals are supported with exceptions funding, particularly those suggesting novel approaches. Expert NCI advisory panels and Progress Review Groups continue to identify priority research and recommend funding. With increased resources in 2004, we will be able to fund the top 35 percent of competing grant applications using flexible criteria and continue to allocate the first 80 to 90 percent of available funds for research project grants through conventional selection processes, while ensuring that proposals from new investigators are also funded.

NCI-supported **Centers, Networks, and Consortia** encourage the interdisciplinary collaborations needed to address the "big picture" problems in cancer research and integrate clinical observations with research investigation. The rapid pace of scientific and technological discovery requires that scientists of diverse backgrounds work together to share information and resources. In 2004, NCI will use new funding to increase the number and geographic distribution of Cancer Centers, providing service to regional communities in addition to expanding crosscutting research capacity. Cancer Centers will serve as platforms to support new technology development, improve informatics capabilities, and conduct more clinical and population research. Specialized Programs of Research Excellence will be expanded based on needs for disease-specific translational research. Underserved and minority populations will have improved access to the newest trials and state-of-the-art care through partnerships with NCI-designated Cancer Centers, Minority-Serving Institutions, and NCI Special Populations Networks.

NCI's **National Clinical Trials Program in Treatment and Prevention** provides a versatile system to safely move emerging cancer interventions into health care delivery. NCI's challenge is to provide the leadership demanded by the emerging paradigm of molecular targeted therapy in cancer treatment and prevention. With adequate funding in 2004, NCI will be poised to identify the most important questions that can be addressed through clinical trials; create the flexible mechanisms and support that will bring together basic scientists and clinicians to find the answers; fund tissue and specimen banks; help develop surrogate endpoints for use in small translational trials; move the most promising interventions into large and easily accessible trials; and simplify administration activities while increasing patient accrual, to substantially increase the number of new treatments and other interventions being evaluated. With sufficient funding, we can make state-of-the-art clinical trials and the ensuing discoveries available to all who can benefit from them.

Bioinformatics for Cancer Research will help us harness the growing flood of scientific information using NCI's systems for resource sharing and for translating pioneering research into better medicine. Virtual experiments will use data from multiple sources. We will generate hypotheses and create and manage more knowledge faster with systems that standardize, support, and integrate information from our diverse research. caCORE, a standards-based cancer knowledge resource, makes possible "in silico" experiments with the Cancer Models Database, Cancer Genome Anatomy Projects, and the Cancer Therapy Evaluation Program. For example, participants in the Cancer Molecular Analysis Project locate and assess possible molecular targets, find therapeutic agents, screen for toxicity, and identify clinical trials. Bioinformatics holds impressive potential for facilitating cancer diagnosis, as demonstrated in the recent marriage of proteomics and artificial intelligence that resulted in a promising ovarian cancer-screening test. In 2004, NCI will use new funds to expand our own informatics infrastructure and the informatics capacity of the research community.

Advancing Discovery and Its Application

Increased investment in broad scientific opportunities and emergent fields of research that lie beyond the size and scope of our current research activities allow us to accelerate the pace of discovery. Better understanding our audiences and their needs allows us to facilitate application of research results in the clinic and public health programs, to benefit all people affected by or at risk for cancer.

The study of **Genes and the Environment** increases our understanding of the interplay between individual inherited susceptibility to cancer and environmental risk factors, enabling the development of more effective approaches to cancer prevention, early detection, and treatment. NCI is investing in this area through large-scale collaborations, such as the Cohort Consortium, by bringing epidemiologists, genomicists, and other investigators together to pool data and resources for large population studies. NCI Cancer Family Registries provide resources for the characterization of predisposing genes found in families at high risk for cancer. In 2004, NCI will use new funding to identify additional environmental risk factors and susceptibility genes and determine their interactions in cancer causation; identify genes in high-risk families and investigate how other genes and environmental factors modify them; and support collaborative studies of the clinical, behavioral, and societal issues associated with cancer susceptibility.

All cells have "molecular signatures" – unique, identifiable characteristics related to a cell's function in the body. As a normal cell becomes malignant, its signature changes and this change becomes a signal of the presence of cancer. Research on **Signatures of the Cancer Cell and Its Microenvironment** focuses on identifying the signatures of both cancer cells and "co-conspirator" cells in the surrounding microenvironment that interact with cancer cells to encourage tumor growth. With new technologies, scientists are reading cancer-associated signatures and using this information to detect cancers at their earliest stage, to diagnose and classify tumors according to their molecular profiles, and to devise treatments that selectively target molecular signatures. Several large initiatives are already making important progress in these areas. New funding in 2004 will be used to define and characterize the molecular signatures of cells in the cancer microenvironment at various points during cancer initiation and progression; to define how communication among cancer cells, surrounding cells, and immune cells controls or promotes tumor growth; and to create targeted interventions based on this new knowledge.

Our ability to decipher the molecular basis of cancer has launched an exciting new era in biomedical research as we hone in on **Molecular Targets of Prevention and Treatment.** Researchers are directing a new generation of low toxicity, high efficacy agents against the molecular features, or targets, that cause tumor growth. NCI is using a multi-disciplinary approach to discover ways to trigger the cancer cell to revert to normal, stop replicating itself, or self-destruct. Other strategies harness the immune system to combat the cancer or prevent surrounding tissues (the "tumor microenvironment") from supporting cancer growth. NCI will use new funding in 2004 to characterize potential targets; support basic and clinical research to validate drugs developed to hit the targets and move them into clinical use; investigate combinations of radiation therapy with molecular therapeutics; and develop the next generation of cancer vaccines. This work will speed development of interventions against cancer, based on the unique molecular characteristics of each patient's tumor.

Investment in **Cancer Imaging and Molecular Sensing** has dramatically improved cancer detection, diagnosis, and treatment. Experimental, molecule-size biosensors that can be injected into the bloodstream promise even more options for patient care. NCI's challenge is to improve imaging and biosensor technologies to ensure earlier, more accurate cancer diagnoses, individualize therapies, use fewer invasive interventions, and improve patient monitoring. Accordingly, NCI is improving functional imaging, developing molecular and digital imaging databases, building micro-imaging techniques for animal research, and supporting biosensor research. Through clinical trials and public-private partnerships, we are moving promising imaging advances from discovery and development to clinical use. With new funding in 2004, NCI will be able to expand development of novel imaging agents and devices; increase clinical trials of imaging technologies, such as the National Lung Screening Trial; integrate functional imaging methods into therapeutic clinical trials; advance

image-guided interventions; and stimulate research on biosensors. Significant advances in these areas will increasingly save and improve lives.

Cancer Communications empowers people to make informed cancer-related decisions and adopt behaviors to improve their health. NCI is working to optimize the use of communications tools to meet the information needs of all groups while building strategies to enhance the important interaction between patients and their doctors and nurses. Lives are saved through communication interventions that decrease or prevent smoking, influence good nutritional choices, and increase the number of people who are screened to detect cancer early. Enhanced NCI databases and Web sites include user friendly topical formats and clinical trials information. In 2004, NCI plans to establish new data collection and analysis strategies, including the first national health communications survey of U.S. populations; accelerate the pace of research and development of communications interventions; increase access to and use of cancer information; and improve our understanding of and ability to effectively move research results into clinical practice and public health programs.

Addressing Areas of Public Health Emphasis

Progress against cancer takes place not only in the laboratory and the physician's office, but also within broad public health programs. NCI has identified four areas to more fully address cancer care and its consequences and translate research into full application for people affected by cancer.

Improving the **Quality of Cancer Care** is a major national concern. Barriers to high quality care include system and financial limitations, proximity of healthcare facilities, available education and information, and physician and patient biases. To address these concerns, NCI is helping to ensure that the best available scientific evidence guides cancer care decision making. NCI is supporting the Cancer Care Outcomes Research and Surveillance Consortium and other studies to strengthen the science base for understanding palliative care and symptom management and end-of-life distress as well as examining depression in cancer patients. With funding increases in 2004, NCI will engage in activities to improve methodology and measurement of patient outcomes; support innovative research on the diffusion, quality, and outcomes of cancer interventions and its translation to best practices in patient care; enhance quality-of-care research within the NCI clinical trials program; strengthen cancer communications; and inform science-based Federal decision making.

Effectively **Reducing Cancer-Related Health Disparities** requires new understanding to explain social, cultural, environmental, biological, and behavioral determinants of cancer, the interactions among them, and the mechanisms by which they contribute to disparities in cancer care and prevention. NCI continues to address disparities among all population groups through numerous initiatives such as the establishment of new centers focused on disparities research, the Cancer Prevention Fellowship Program, and the implementation of a landmark study to determine factors that contribute to cancer among groups hardest hit by the disease. In 2004, we will use funding increases to expand our research on the causes of health disparities in cancer; define and monitor disparities; develop and implement new policy, community, and clinical interventions, and evaluate their impact; and expand minority investigator competition for, and minority population involvement in, health disparities research and clinical trials.

Through statistics on **Cancer Survivorship,** we are beginning to see the fruits of the "War on Cancer" launched in 1971. Once almost uniformly fatal, cancer has become a chronic illness for many and, for growing numbers of people, a curable disease. Fewer deaths from other diseases and the aging of the population also contribute to the rising number of cancer survivors. However, we have many questions about the health status and quality of life for most patients in their post-treatment years. What is clear is that most of our current treatments will produce some measure of adversity. NCI is initiating a focused effort in 2004 to understand the mechanisms that affect a cancer patient's response to disease, treatment, and recovery; develop tools to assess quality of life following treatment; track outcomes for cancer survivors; disseminate clinical guidelines; and expand the scientific base for understanding the adverse late effects of current and new cancer treatments.

Research on Tobacco and Tobacco-Related Cancers is driven by the devastating impact of tobacco use and tobacco exposure on the incidence of cancer. Tobacco use causes more premature death (approximately 430,000 per year in the United States) than do all drugs of abuse combined. NCI research is focused on improving understanding of tobacco-related addiction and carcinogenesis, including the role of genetic and environmental factors in smoking initiation, persistence, and relapse. Through several new initiatives, including the Lung Cancer Screening Study as well as preclinical and clinical studies to identify more potent agents for cancer prevention, NCI-supported research is targeting the health needs of current and former smokers. NCI will use new funds in 2004 to expand the infrastructure needed to conduct a vigorous research program; support investigations to understand and treat tobacco use and addiction; and apply cutting edge research to better understand and treat tobacco-related cancers.

Planning at NCI Includes the Larger Cancer Community

Each year, countless people at NCI, on our advisory boards, in other government agencies, and in research, professional, and advocacy organizations around the country provide their insights, perspectives, and expertise for the development of this document. Members of the Office of Science Planning and Assessment provide leadership and guidance for plan development from conceptualization to production. They work alongside the core group of NCI leaders who serve as Champions for the various priority areas and with the Office of Budget and Financial Management. Numerous other people at NCI review drafts, provide background information, and identify new areas to explore. In 2001, some 40 individuals and organizations inside and outside NCI responded to our sweeping solicitation to the cancer community for suggestions about new scientific priority areas (Extraordinary Opportunities). In the summer of 2002, a similar number of people outside of NCI responded to our request for input to a draft of this document. All of these contributions have been invaluable in helping us develop a plan for Fiscal Year 2004 that captures the opportunities, challenges the community to new heights, and brings us closer to our goal to control or eliminate all cancers. See page 100 for our acknowledgments list of people and organizations who contributed to this document.

NCI's Budget Request for Fiscal Year 2004

(dollars in thousands)

Fiscal Year 2003 President's Budget	$	4,637,869
Increase to Core Budget		294,014
Capacity Building Increase		
Enhancing Investigator-Initiated Research		69,887
Expanding the Capacity of Centers, Networks, and Consortia		79,530
National Clinical Trials Program in Treatment and Prevention		340,100
Developing Bioinformatics for Cancer Research		88,000
Subtotal Capacity Building		577,517
Discovery and Application Increase		
Genes and the Environment		51,800
Signatures of the Cancer Cell and Its Microenvironment		41,200
Molecular Targets of Prevention and Treatment		54,800
Cancer Imaging and Molecular Sensing		78,700
Cancer Communications		39,750
Subtotal Discovery and Application		266,250
Public Health Emphasis Increase		
Improving the Quality of Cancer Care		27,000
Reducing Cancer-Related Health Disparities		61,350
Cancer Survivorship		46,000
Research on Tobacco and Tobacco-Related Cancers		76,000
Subtotal Public Health Emphasis		210,350
Total FY 2004 Budget Request		**$5,986,000**

Highlights of Progress

Every year thousands of NCI-supported research projects move us closer to a time when cancer can be controlled or eliminated. The recent doubling of NCI's budget has been instrumental in funding numerous studies across the cancer continuum and from fundamental laboratory research to patient care. These highlights of recent progress provide a snapshot of the breadth of our research advances.

Trends in Research and Care

NCI Releases the Cancer Progress Report. To build on areas of greatest success and pinpoint areas of greatest need, NCI is working with many partners to stay abreast of progress in cancer research and care in the United States. NCI's ***Cancer Progress Report***,[1] first published in December 2001, describes the Nation's progress in reducing the cancer burden, encompassing the continuum from prevention to deaths from specific cancers. Also reflected are declines in certain behaviors that cause cancer, especially cigarette smoking by adults. More people are getting screened for breast, cervical, and colorectal cancers, and more practitioners are adopting state-of-the-art cancer treatments. At the same time, work needs to be done to reduce rates of some cancers that are still on the rise. These include non-Hodgkin's lymphoma, melanoma, cancers of the liver and esophagus, as well as breast and lung cancer in women. Greater efforts also are needed to reduce tobacco use, weight gain, and sun exposure and to increase physical activity. We must also redouble our efforts to eliminate persistent cancer-related health disparities among population groups.

Changing Age Structure of the United States Will Help Guide the Future of Cancer Research and Care. ***The Annual Report to the Nation on the Status of Cancer, 1973-1999,*** *Featuring Implications of Age and Aging on the U.S. Cancer Burden*,[2] was released in May of 2002. The report is encouraging. Overall cancer death rates decreased from 1993 to 1999, while rates of cancer incidence stabilized over a similar timeframe. However, trends in various populations groups differed substantially — e.g. by cancer site, sex, and race. Most notably, because of increasing population and the growing proportion of older persons, researchers expect the cancer burden in the United States to increase substantially over the next several decades. Our changing age structure will require aggressive strategies for cancer prevention and early detection, social support, treatment and medical care, clinical trial design and enrollment, research, and surveillance. In addition, access to supportive, palliative, and general medical services must be optimized.

Prevention and Control

Smoking Cessation Drug May Help Address Smoking-Related Health Disparities. In a recent landmark study, investigators found that bupropion, a promising smoking cessation drug previously studied mostly in White populations, is effective in helping African Americans quit smoking. Bupropion also seemed to curb both weight gain and feelings of depression among study participants, key indicators of whether a person will return to smoking. The success of this treatment is especially significant given that smoking rates are higher for African Americans than for the overall population of the United States. For example, close to half of African Americans who live in inner cities smoke compared to about one quarter of the general population. Smoking is the leading cause of lung cancer and a major risk factor for other cancers as well as heart disease, respiratory disorders, and other diseases prevalent in African American groups. Researchers hope that a successful smoking cessation program, aided by bupropion, may help reduce smoking-related health disparities experi-

[1] **progressreport.cancer.gov**

[2] Prepared by the National Cancer Institute, the Centers for Disease Control and Prevention, the National Center for Health Statistics, the American Cancer Society, and the North American Association of Central Cancer Registries. **seer.cancer.gov/reportcard**

enced by African Americans as well as the overall cancer burden caused by tobacco use.

Potential of Dietary Aids for Cancer Prevention Is Complex. Over the years, many studies have examined how what we eat or drink affects our risk of developing cancer. The sometimes conflicting results point to the need for large, careful studies to clarify some of these findings. In one recent study, with tens of thousands of participants, investigators discovered that both men and women could reduce their risk of developing cancer of the distal colon by consuming high levels of calcium daily. A similar study showed that high levels of calcium and dairy products substantially increase the risk for prostate cancer, while lycopene, a component of tomatoes, provided some protection against prostate cancer. The finding that calcium can reduce the risk of one cancer while increasing the risk of another illustrates the complexity of the interaction between diet and cancer. Further study is needed before clear advice can be communicated to the public about the usefulness of calcium for cancer prevention.

Oophorectomy after Childbearing Years Lowers Cancer Risk in Women with *BRCA* Mutations. Women who were born with certain mutations to the genes *BRCA1* and *BRCA2*, are more likely to develop breast and/or ovarian cancer, and at a younger age than the general population. Based on the findings of a number of small studies, physicians have been recommending that women with these mutations undergo prophylactic oophorectomy (removal of the ovaries), once they have finished having children. Recently completed large studies have validated this practice to reduce cancer risk. In an NCI-supported study, ovarian cancer risk was reduced by a striking 96 percent and breast cancer risk was reduced by about 50 percent. Side effects brought on by premature menopause are manageable by medication. The researchers found no evidence to suggest that the ovaries should be removed before the childbearing years.

Other cancer prevention and control highlights in this document:

- Genetic signatures and risk factors for pancreatic cancer, page 21
- Risk factors for esophageal cancer, page 23
- Arthritis drug and prevention of colon polyps, page 36
- Aspirin for preventing colon cancer, page 40
- Genetic signature and effectiveness of bupropion, pages 94-95
- Key factors in adolescent cigarette use, page 95

Detection, Diagnosis, and Prognosis

New Blood Test for Early Detection of Prostate Cancer Looks Promising. To screen for prostate cancer, doctors currently use a blood test to measure the levels of a protein called prostate-specific antigen (PSA), which is consistently elevated in men with prostate cancer. However, since PSA is sometimes elevated even in the absence of cancer, a follow-up biopsy must be performed if the PSA test is positive. The PSA test is quite helpful to many men by detecting their cancer in its earliest stages. The down side is that a number of men without the disease are subjected to biopsy, and associated anxiety, to rule out cancer. To address this concern, researchers used the emerging technology of protein profiling[3] to fashion a new blood test. The new test uses computer-based artificial intelligence to study the dynamic patterns of nine separate proteins in the blood. In preliminary study, this test correctly identified most men with prostate cancer and misclassified far fewer men without the disease than could be hoped for with the PSA test. With further development, this new test may lead to a more accurate means to detect and diagnose prostate cancer at a very early stage, with fewer false positives and unnecessary biopsies.

SPORE[4] Study Suggests New Molecular Test Useful for Prognosis of Colorectal Cancer. To estimate the chance that colorectal cancer might recur after surgery, health professionals must examine small amounts of tumor tissue under the microscope. This is called histopathological staging. Many scientists are looking for molecular markers, such as suspicious abnormalities in tumor DNA, to develop a more reliable prognostic tool. Previously, scientists discovered that patients with allelic imbalance[5] in certain chromosomes of the tumor tend to have a poorer prognosis. Until recently, however, it has been very difficult to accurately measure allelic imbalance in tumor tissue. Now, investigators have

[3] For more information on protein profiling, see page 54.

[4] Specialized Programs of Research Excellence. For description see page 32 .

[5] Chromosomes come in pairs that are typically nearly identical in makeup. For example chromosome 8p and chromosome 8q together comprise what we call "chromosome 8." Sometimes errors occur that make one chromosome of a pair substantially different from the other. This is known as "allelic imbalance."

developed a highly sensitive test using a technique called "digital SNP analysis." This new test measures the allelic imbalance in two colon cancer-associated chromosomes, 8 and 18. They found that, after five years of follow up, cancer recurred in 42 percent of patients with allelic imbalance in both chromosomes and in 26 percent of those with one chromosome affected. In contrast, all patients with no detectable allelic imbalance in chromosomes 8 or 18 remained disease free after five years. Since routine histopathological staging would have mistakenly predicted recurrence in at least some of these disease-free patients, this new test appears to provide an improved prognostic indicator of colorectal cancer. Further research must be done to show whether this technique will work as well for other cancer sites.

Ovarian Cancer patients with *BRCA* Mutation Have Better Survival than Non-Carriers. Women who inherit mutations to the *BRCA1* or *BRCA2* gene, have a greater risk of developing ovarian cancer. However, until recently, researchers could not predict whether women with these mutations would fare better, the same, or worse than other women with ovarian cancer. To examine this issue, researchers studied the medical records of almost 900 newly diagnosed ovarian cancer patients with inherited *BRCA* mutations and followed their progress for five years.[6] Investigators compared the progress of these women to that of patients who had no *BRCA* mutation. On average, the patients with *BRCA* mutations survived for about 53.4 months, almost 20 months longer than women without the mutations. This survival advantage was not due to earlier detection, but seems to reflect a difference in the pattern of the disease in women with and without *BRCA* mutations. The mechanism of this phenomenon is not known. Further follow up in this continuing study should reveal whether the better survival of *BRCA* mutation carriers is long-term or limited to the first few years of the disease.

Other detection, diagnosis, and prognosis highlights in this document:

- Genetic signatures and diagnosis of acute lymphoblastic leukemia, pages 44 and 54
- Blood test of protein patterns and early detection of ovarian cancer, pages 45, 54, and 59
- Gene expression array for prognosis of diffuse large-B cell lymphoma, page 54
- Signatures of lung cancer sub-classes, page 59

Treatment

New Approach to Immunotherapy for Advanced Melanoma Results in Dramatic Tumor Regression. In a recent study of melanoma[7] patients, researchers discovered a way to enhance the immune system's natural, but weak, ability to attack cancer cells. Investigators began by collecting a small number of white blood cells from the tumors of each of 13 patients. From these, they isolated the cells that were most adept at attacking melanoma — those that could best recognize an antigen[8] abundantly expressed on melanoma cells and to a lesser extent on normal melanocytes. They grew large quantities of these white blood cells and injected them back into each patient along with an immune-boosting protein. To prevent the patient's naturally occurring white blood cells from crowding out the melanoma-attacking cells, investigators temporarily depleted the patient's immune system with chemotherapy prior to injection. With this treatment regimen, six patients experienced dramatic regression of metastatic tumors. Surgeons removed the traces of tumors from two of these patients who have remained cancer free, one for over two years. In some patients, the melanoma-killing cells also attacked normal melanocytes, resulting in patches of skin without pigmentation (a non-threatening condition known as vitiligo). Other side effects were treatable. This pioneering study establishes two landmark principles of cancer research. First, this unique approach to harnessing the immune system can be an effective treatment for patients with metastatic cancer. Secondly, naturally occurring antigens that are over-expressed on cancer cells may provide useful immunotherapy targets for cancers such as prostate, breast, ovarian, and thyroid, since the organ function is either not necessary for survival or can readily be replaced.

[6] The study was performed in Israel where more women have the mutations, making it easier to conduct a large study.
[7] Melanoma is cancer of the melanocytes, the pigment producing cells of the skin. It is almost always fatal once it spreads beyond the initial site.
[8] An antigen is a protein or protein fragment located on the outside of a cell.

SPORE Scientists Find Ways to Overcome Resistance to Tamoxifen for Breast Cancer Treatment. A subclass of breast cancer known as "estrogen receptor positive" (ER-positive) grows more aggressively when exposed to estrogen. The drug tamoxifen works well against ER-positive breast cancer by lowering estrogen levels in the body. However, scientists have been faced with the puzzle of why some women never respond to this drug and why in those who are helped, it often works only for a limited time. Also, high levels of a certain protein, HER-2, seem to make tumors more resistant to tamoxifen, but only in some women. In studying these problems, researchers found that another drug, fluvestrant, works against tumors that don't respond to tamoxifen. Investigators also discovered that HER-2, by itself, does not interfere with tamoxifen. Only in women where HER-2 and a second protein, AIB1, are simultaneously elevated, were tumors resistant to tamoxifen. This research on the mechanisms of tamoxifen resistance is yielding new, more effective treatment approaches. The United States Food and Drug Administration recently approved fluvestrant for treatment of tamoxifen-resistant, ER-positive breast cancers, and scientists anticipate that further research on HER-2 and AIB1 may open highly promising avenues for both diagnostic and therapeutic interventions.

Molecularly Targeted Drug Slows Tumor Growth in Patients with Kidney Cancer.[9] Researchers have identified another promising molecularly targeted[10] cancer treatment drug. In a recent clinical trial, the drug bevacizumab significantly slowed the growth of metastatic renal cancer in patients with advanced disease and no known treatment options. Patients given this drug showed no measurable tumor growth for about five months, as compared to two months in patients taking a placebo. Bevacizumab targets a protein, called VEGF, needed by the tumor to generate new blood vessels (angiogenesis) to bring oxygen and nutrients for growth. This study is an important first step toward showing that recent exciting laboratory advances in attacking cancer by thwarting angiogenesis will work in patients. More than 20 additional clinical trials are currently underway to evaluate bevacizumab as a cancer treatment, including Phase III trials for breast and colorectal cancers and Phase II trials for prostate, breast, colorectal, cervical, ovarian, pancreatic, and lung cancers, mesothelioma, and several types of leukemia.

Experimental Drug Improves Survival of Patients with Advanced Colorectal Cancer. Researchers conducting a large clinical trial have discovered a new chemotherapy drug that, in combination with current drugs, appears to improve the survival of colorectal cancer patients. Patients with advanced colorectal cancer who were treated with the "FOLFOX4 regimen" (which includes the experimental drug oxaliplatin), lived about four months longer than patients receiving standard therapy, the "Saltz regimen."[11] Patients treated with FOLFOX4 responded better to their medication and tumors were slower to progress. Although many patients developed a neurotoxicity not seen with the Saltz regimen, severe side effects were significantly fewer overall. Furthermore, 71 percent of patients on FOLFOX4 were living after one year, compared to 58 percent of those on the Saltz regimen. These results are impressive for a disease that is the second leading cause of cancer death in the United States. As further tests are being conducted, the manufacturer of oxaliplatin is submitting data to the United States Food and Drug Administration for possible use of this drug as a second-line treatment for colorectal cancer.

Other treatment highlights in this document:

- Tamoxifen following chemotherapy and breast cancer patients, page 37
- Methotrexate and T-cell acute lymphoblastic leukemia survival, page 37
- Gleevec (imatinib) and chronic myelogenous leukemia, page 37
- Gleevec (imatinib) and GIST, page 37
- Immunotoxin and hairy cell leukemia, page 64

[9] See also page 22.

[10] Molecularly targeted drugs are designed to interact with and disrupt certain molecular features that are critical to the survival of the cancer cell, without harming healthy tissues.

[11] FOLFOX4 regimen: 5-fluorouracil/leucovorin/oxaliplatin Saltz regimen: irinotecan/5-fluorouracil/leucovorin

Understanding the Causes of Cancer

SPORE Scientists Say Inherited *BRCA2* Mutations May Increase Risk for Pancreatic Cancer.[12] Scientists believe that 10 percent of all cases of pancreatic cancer are hereditary. However, although mutations have been found in the tumors of patients with non-hereditary pancreatic cancers, the major gene(s) responsible for inherited cases have yet to be discovered. Uncovering the causal mutations would provide a way to identify people who might benefit from special surveillance because of an increased genetic risk of developing this disease. In a recent study, investigators searched for suspicious mutations in the *BRCA2* gene of pancreatic patients who had at least three relatives with this disease. They discovered mutations likely to be involved in tumor development in 5 out of 29 (or 17 percent) of patients in the study. Further research is needed to better define the risk of pancreatic, and other cancers, in patients with these mutations. Additional genetic as well as environmental factors may influence this risk.

SPORE Study of Tumor Microenvironments Yields New Insights into Cancer. Unique molecular interactions occur between cancer cells and their surrounding tissues, the "tumor microenvironment." For example, when healthy tissues of the body are invaded with cancer cells, they become inflamed and form fibrous, scar-like tissue — known as "desmoplastic tissue." In certain tumors that penetrate into surrounding tissues as they grow (known as infiltrating tumors), this desmoplastic tissue comprises the bulk of the tumor, outpacing the actual cancer cells. Recently, a team of scientists characterized the patterns of genes expressed in the cancerous growth and the microenvironment of two types of infiltrating cancer — pancreatic and infiltrating breast cancer. They discovered a highly ordered, coordinated process of tumor invasion, involving four distinct kinds of tissue and structured molecular interactions between the cancer and its surrounding tissues. This kind of insight into how cancers interact with their microenvironment may lead to previously unimagined strategies for imaging, diagnosis by blood test, and drug development and delivery for pancreatic, infiltrative breast, and numerous other cancers.[13]

Gene-Environment Interactions Are Identified for Non-Hodgkin's Lymphoma. Despite much research, the relationship between exposures experienced by farm workers and non-Hodgkin's lymphoma (NHL) is unclear. However, past studies did not consider gene-environment interactions that might occur in some genetic subtypes of this disease. Because of the way statistical analysis works, when the genetic subtypes of NHL are not studied individually, real associations between farming exposures and NHL might remain hidden. Investigators recently reviewed the exposure data and studied NHL biopsies from about 200 patients who had participated in a prior study. These researchers were able to identify a particular genetic subtype of NHL that appears to be susceptible to the effects of pesticides. Larger studies are needed to clarify the mechanisms behind this gene-environment interaction and to discover ways to intervene to prevent NHL.

Survivorship

African American Cancer Survivors Report Poorer Functional Health than Whites. Older and minority patients have been underrepresented in research of post-cancer treatment issues. Investigators interviewed 180 African American and White long-term breast, colorectal, and prostate cancer survivors to identify differences in reported health problems, illness symptoms, functional difficulties, health worries and concerns, and overall perceptions of health. Although African Americans did not report significantly more symptoms resulting from their cancer or its treatment, they did report a greater decrease in physical functioning, perhaps related to treatment. Older African Americans also reported less concern about development of second cancers, suggesting a need for targeted education about the importance of follow-up care and screening. Continued research is needed to understand post-cancer treatment issues among older and minority patients.

Adult Survivors of Childhood Cancer Lack Detailed Knowledge of Their Past Illness. Childhood cancer cure rates have risen dramatically over the past few decades, creating a growing body of adult survivors who face long-term health risks related to their cancer and treatment. Researchers interviewed 635 adult survivors of childhood cancer to find out how much they knew about their

[12] See also page 21.
[13] See also Signatures of the Cancer Cell and Its Microenvironment, pages 55-59.

previous illness and treatment. None of the survivors were able to give a detailed summary of their disease, including the name of their cancer, whether they received certain chemotherapy drugs, and the site or sites of radiation treatment. Only 35 percent of those interviewed realized that past treatments could cause serious health problems in the future. Such missing information could prevent survivors from understanding their need for special follow-up care and surveillance. This study highlights a need for educating childhood cancer survivors about their past illness and how it was treated.

Smoking Rates Characterized among Childhood Cancer Survivors. Researchers are working to characterize smoking patterns among childhood cancer survivors, who are at high risk for tobacco-related health problems. A recent survey of almost 10,000 adult survivors of childhood cancer showed that, although these survivors were less likely to smoke than the general population, 17 percent were current smokers, and 11 percent were former smokers. Survivors who had been diagnosed with cancer in later childhood were more likely to start smoking, as well as those with a lower household income and/or less education. African Americans and survivors having had either pulmonary related cancer treatment or brain radiation were less likely to smoke. Among survivors who did start smoking, some were more likely to continue smoking: those who were at least thirteen years old when beginning to smoke, those with less education, and those who had brain radiation. The information gained by this research will help craft needed interventions to prevent smoking and to promote quitting in this high-risk population.

Other survivorship highlights in this document:

- Tool used for studies on the consequences of cancer treatment, page 92
- Chemotherapy dosage and congestive heart failure, page 92
- Lung cancer survivor quality of life, page 92
- Growth hormone replacement for children following treatment for leukemia, page 92
- Social interventions for breast cancer survivors, page 92

Quality of Cancer Care

Racial and Ethnic Minorities Receive Less Appropriate Cancer Treatment. Racial and ethnic minorities in the United States bear a disproportionate burden of invasive cancers and cancer deaths. African Americans, for example, are more likely to develop a number of cancers and are 33 percent more likely than Whites to die of cancer. Hispanics are more likely to develop cervical cancer, and Asian/Pacific Islanders to develop stomach cancer. A group of investigators extensively reviewed published scientific studies to find out whether any of these disparities stem from access to or use of specific cancer treatments. Their review confirmed that racial differences are evident in who receives the best available primary, conservative (such as breast conserving), and adjuvant therapies. Those receiving inferior therapy were also more likely to relapse and die. These disparities could be explained in part by non-clinical factors, such as socioeconomic status, patient concerns about body image, age at diagnosis, the size of the hospital where surgery is performed, the number of previous surgeries performed by the surgeon, geographic location, and insurance coverage. Patient preferences and decisions also played a part.

Rate of Complications from Prostate Surgery Decreases with Number Performed. For many cancers requiring surgery, patient survival is better when the surgery is conducted at hospitals and/or by surgeons that perform the highest volume of this operation. Although this is not true for patients receiving prostate cancer surgery, for which survival is high overall, researchers wondered whether the choice of hospitals or surgeons might affect postoperative morbidity (e.g. urinary complications, incontinence). Investigators discovered that those men who underwent removal of the prostate at hospitals and by surgeons who performed a high volume of this surgery, experienced fewer postoperative and late urinary complications. The researchers point out a need for more careful scrutiny of adverse outcomes to reduce the burden of suffering among patients who undergo surgery for prostate cancer.

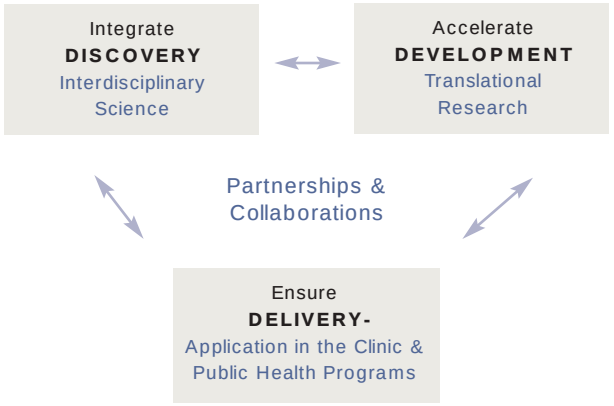
Other quality of care highlights in this document:

- Social factors and survival among African American patients with advanced non-small cell lung cancer, page 85
- Educational interventions and cervical screening within the Chinese-American population, page 85
- African American men and risk for advanced prostate cancer, page 85

Our Role in Cancer Research

The National Cancer Institute's goal is to achieve a future when all cancers are controlled or eliminated by stimulating and supporting scientific discovery and its application. As the leader of the National Cancer Program, we provide vision and leadership to the cancer community. We work to:

- More fully integrate **discovery** activities through interdisciplinary collaborations.
- Accelerate **development** of interventions and new technology through translational research.
- Ensure the **delivery** of these interventions for application in the clinic and public health programs.



Scientific Discovery

NCI supports a broad range of research to expand scientific discovery at the molecular and cellular level, within a cell's microenvironment, and in relation to human and environmental factors that influence cancer development and progression, and the patient experience. These insights provide the platforms on which to accomplish improvements in prevention, control, early detection and diagnosis, treatment, and post-treatment care.

Each year, almost **5,000 principal investigators lead research projects** that result in better ways to combat cancer. These scientists conduct studies at NCI and at nearly 650 universities, hospitals, and other sites in nearly every state in the Nation and in more than 20 foreign countries. Intramural research activities serve as hubs for new development through cutting edge basic, clinical, and epidemiological research. Extramural program experts provide guidance and oversight for research conducted at universities, teaching hospitals, and other organizations. Proposals submitted by extramural investigators are selected for funding by peer review, a rigorous process by which scientific experts evaluate new proposals and recommend the most scientifically meritorious for funding.

Some studies involve basic laboratory research on genomics, proteomics, and molecular interactions. Others help us gain understanding of cancer in specific populations, such as former smokers, to better understand cancer risks related to environmental and lifestyle factors.

In addition to direct research funding, NCI offers the Nation's cancer scientists a variety of useful **research services and tools**. NCI-supported Cancer Centers and Centers of Research Excellence such as the *In Vivo* Cellular and Molecular Imaging Centers and the Centers of Excellence in Cancer Communications Research provide the kind of interdisciplinary environments required for special projects. The Transdisciplinary Tobacco Use Research Centers are supporting a broad array of studies on nicotine addiction and genetic and environmental factors related to smoking. Resources such as tissue samples, statistics on cancer incidence and mortality, databases of genetic information, imaging databases, and software for analyzing statistical and genetic data[1] are made available at little or no cost. Consortia like the Mouse Models of Human Cancers Consortium allow scientists from around the world to share their expertise and resources in creating strains of mice that develop cancers similar to those seen in humans, making widely available an invaluable tool for cancer researchers.

[1] For a directory, go to **cancer.gov/resources.**

Ongoing Research Shows Value of Centers of Research Excellence, Networks, and Consortia

Specialized Programs of Research Excellence (SPOREs), other Centers of Research Excellence, and NCI-support networks and consortia provide opportunities for research that cannot be conducted by investigators at single institutions.

- **Breast Cancer SPOREs** are testing the use of imaging and gene array assessments to find markers that predict long-term response to chemotherapy before breast cancer surgery. These kinds of techniques may allow patients and their physicians to make more confident decisions to use the therapy as well as to help identify patients who are likely to relapse and may wish to consider other options.
- **Ovarian Cancer SPOREs** are participating in a screening trial to test the efficacy of obtaining periodic CA 125 values and to determine if this screening method, along with transvaginal ultrasounds, is effective for early detection in women at high risk for ovarian cancer. The trial is being conducted through collaboration with the Cancer Genetics Network.
- **Prostate Cancer SPOREs** have worked together to develop the necessary infrastructure to validate relevant biomarkers for prostate cancer using high throughput analysis and technologies that will ultimately bring into clinical practice new biomarkers for diagnosis, prognosis, and treatment. Additionally, the prostate SPOREs are developing microarrays for studies on special populations including African Americans, Hispanics, and Asian Americans.
- **The Chronic Lymphocytic Leukemia (CLL) Research Consortium**, a multi-institutional research program, brings together the nation's top scientists from different disciplines to conduct an integrated program of basic and clinical research focused on a single disease. CLL is the most common, and currently incurable, adult leukemia. Nine institutions are engaged in six research projects. Five are laboratory based and the sixth is a multicenter program to conduct clinical trials of promising new agents.
- Two adult brain tumor consortia, the **New Approaches to Brain Tumor Therapy CNS Consortium** and the **North American Brain Tumor Consortium,** have greatly expanded the clinical research agenda for therapy in adults with gliomas and are considered the primary focus nationally for most new agent trials in adult brain tumors. These consortia have successfully evaluated the efficacy and pharmacokinetics of NCI-sponsored agents and incorporated molecular and biological analyses in clinical trials of novel agents aimed at specific molecular targets. Both consortia have established collaborations with industry sponsors.

Intervention Development

In addition to promoting integration and the interdisciplinary environment required to support today's cancer scientists, NCI also uses **collaborative platforms for translational research and intervention development**. Translating basic research into interventions almost inevitably means developing new technologies or transforming those that we have been using. Thus, a new tool that first helps us to understand cancer may eventually be improved and distributed to help us diagnose it, and then may be advanced further still to help us treat it. For example, recent advances in bioinformatics and the related explosion of technology for genomics and proteomics research are dramatically accelerating the rate with which we can process large amounts of information for cancer screening and diagnosis. Likewise, new molecular imaging and biosensing technologies are opening doors to faster, more accurate detection and diagnosis, facilitating more accurate image-guided therapies, and making it possible to monitor treatment outcomes in real time. Similarly, nanotechnology promises to further expand the options for precisely detecting, diagnosing, treating, and monitoring cancer.

To ensure that we use public funds to greatest advantage, NCI promotes collaborations that translate scientific understanding to the clinic. The largest such research activity supported by NCI is our **Clinical Trials Program** for testing cancer treatments, diagnostic tools, and interventions for preventing cancer and providing access as early as possible to all who can benefit. With the participation of more than 10,000 medical school and private practice physicians in NCI's Clinical Trials Cooperative Group and Community Clinical Oncology programs, NCI supports over 1,300 clinical trials a year involving more than 200,000 patients.[2]

In the early 1960s, we began one of our longest running partnerships by establishing the **Cancer Centers Program**. Congress encouraged the expansion of the Program to improve the quality

[2] See pages 36-40 or more information about the NCI National Clinical Trials Program.

NCI Team Includes Advisory Groups

Scientists, medical experts, and advocates work together to help shape NCI's policies and programs through a number of standing and ad hoc advisory groups. The National Cancer Advisory Board provides overall guidance for NCI and a final assessment of the research proposals selected for funding through peer review. The Board of Scientific Counselors evaluates the progress, performance, and productivity of the Institute's intramural research programs and scientists through regular site visits to NCI. The Board of Scientific Advisors plays a similar role for NCI's extramural program, reviewing the progress of ongoing programs and providing feedback on proposed new research activities. NCI convenes Progress Review Groups of scientific and medical experts and advocates to examine the research needs and opportunities for specific types of cancer. NCI is also strongly influenced by the President's Cancer Panel. This and other advisory groups provide seasoned assessment of progress and problems in the Nation's effort to reduce the burden of cancer.

In addition to their membership on other NCI advisory groups, advocates advise the NCI Director on broad program and research priorities through the Director's Consumer Liaison Group. Members of this all-consumer advisory committee have provided assistance to the Institute in other ways as well, including gathering suggestions from the advocacy community on survivorship issues, disseminating and promoting cancer trials training, and assisting with various strategic planning efforts. NCI also solicits the advice of patients and their family members through the recently created Consumer Advocates in Research and Related Activities (CARRA) program. Through this program, approximately 200 individuals are available to participate in a wide range of NCI activities. For example, they participate in advisory groups to help assess needs for specific cancers, provide advice on the design of clinical trials, and review education materials.

Go to **deainfo.nci.nih.gov/advisory/boards.htm** for more information on NCI Advisory groups.

of cancer care by bringing cancer scientists and oncologists together in the same setting with patients and their families. Today, two-thirds of the 60 Centers funded by NCI are comprehensive Cancer Centers, so designated because of the breadth and depth of the research conducted by their investigators and their role in public education and outreach.

NCI **Centers of Excellence** are smaller in scale than NCI Cancer Centers and generally focus on one or a few types of cancer or scientific areas. More than 40 Specialized Programs of Research Excellence bring together groups of cancer scientists with specialized expertise to focus on translational research for disease-specific cancers. NCI also brings investigators together for translational research through networks like the Early Detection Research Network, which assembles groups of scientists to identify markers and develop tests to detect early signs of cancer.

Intervention Delivery and Communication

While delivery of most interventions is ultimately the responsibility of healthcare and public health organizations, NCI's role is to ensure that our research findings reach the community and are translated into practices that will make a difference in the lives of people. The results of NCI-supported research consistently provide cancer patients and those who care for them with information, tools, and tests that can be used for **improved cancer interventions** and can help people make better health choices and physicians select treatment options that are more targeted and less invasive and result in fewer adverse side effects. Evidence-based cancer control interventions influence the nature of public health programs to more effectively reduce cancer risk and promote better health practices. For example, once its effectiveness was confirmed in clinical trials, oncologists were quick to adopt the use of tamoxifen in the care of breast cancer patients. Likewise, since studies established the link between diet and cancer risk, more and more of us strive to include five servings of fruits and vegetables in our daily diets.

NCI **programs to reduce the disparities** in the occurrence of cancer, its treatment, and outcomes among various racial and ethnic groups include research into the causes of health disparities and measures to translate research results into better health for groups at high risk for cancer. For example, NCI-supported investigators are using insurance data to examine the extent to which African American, Hispanic, and Caucasian patients are receiving recommended treatments for colon cancer. Researchers are also seeking the causes of disparities

among other underserved groups. In addition, NCI is supporting field tests of smoking cessation and weight control programs targeted to the needs of specific racial and ethnic groups.

NCI has partnered with other state and Federal agencies to work on a number of **projects aimed at improving the quality of cancer care**, such as efforts to raise the rates of colon cancer screening among veterans and the elderly and cervical cancer screening and treatment among lower income populations across the United States.

When NCI-supported research results in discoveries that may lead to **new drugs, novel technologies, or diagnostic tests**, Federal laws encourage universities and NCI to pursue commercialization by licensing the discoveries to industry. In addition, NCI intramural investigators can also collaborate with industry through arrangements known as Cooperative Research and Development Agreements. It is through such an agreement between NCI and a major pharmaceutical company that investigators are following chronic myelogenous leukemia patients treated with the recently approved anti-cancer agent imatinib,[3] to determine its long-term effects.

While major scientific advances typically reach the medical community and the public through medical journals and news reports, NCI proactively disseminates information on new interventions through a range of other **cancer communications activities**. For example, NCI provides Web-based information on cancer and clinical trials, toll-free telephone service in all regions of the country, and printed brochures and educational packages distributed directly to consumers and through physicians and advocacy organizations. NCI-supported researchers work to create the best methods for reaching all who need to learn about cancer, with news of recent research findings and information on opportunities to participate in clinical trials.

We also foster collaborations leading to new interventions through **partnerships with other Federal and state agencies** charged with strategic roles in improving the Nation's health. For example, the preponderance of data on cancer trends have been collected and analyzed through the combined efforts of NCI, the Centers for Disease Control and Prevention, and state cancer registries. This information is critical to targeting public health interventions as well as informing our fundamental research hypotheses relating cancer susceptibility and environmental factors. Likewise, partnerships with the Food and Drug Administration and pharmaceutical companies are accelerating the pace with which we are able to move drugs through the pipeline of discovery, development, and delivery.

[3] Also called STI571 or Gleevec.™

Consortium Focuses on Developing Cancer Vaccines

Recent advances in genomics and proteomics have enabled the discovery of novel molecular targets that appear well suited to a vaccine approach, and clinical trials have demonstrated that these vaccines can stimulate the immune system to attack cancer cells while eliminating or limiting toxicity. The approach has had efficacy in early trials in patients with advanced colorectal cancer, renal cell carcinoma, melanoma, and lymphoma. To speed the development of vaccines and their translation to patient care, NCI's Center for Cancer Research has established a Vaccine Initiative to bring together a consortium of scientists with expertise in oncology, vaccinology, and translational research along with representatives of the biotechnology and pharmaceutical industries. Several vaccines developed by consortium members are currently being used in clinical care.

Consortium researchers are also improving the effectiveness of new and existing vaccines by vaccinating with genetically engineered tumor cells to stimulate the immune system, adding genes to the vaccine mixture to produce proteins that are similar to or the same as the target on the cancer cell, and adding molecules to the vaccine mixture that are known to stimulate parts of the immune system.

People don't get "cancer." They develop cancer of the breast, the prostate, the lung, or any of over 100 other types of the disease. The recommendations of Progress Review Groups are central to sustaining the best possible science and making the fastest advances against specific cancers.— *Andrew C. von Eschenbach, M.D.*

National Agendas for Disease-Specific Research

Unlike the common belief of 30 or 40 years ago, we know today that there are more than 100 distinct types of cancer. We are also learning that many diseases have subtypes with unique molecular characteristics that influence how they develop and progress and how they can be effectively prevented, detected, and treated. For these reasons, NCI carries out an ambitious program of research on specific types of cancer. These efforts along with the broad-based programs described in this document provide the framework for national agendas for disease-specific research.

NCI leads the development and pursuit of disease-specific research by assessing the current understanding of specific cancers, the funded research, our ability to prevent and treat the disease, and the extent of our success. We chart the course primarily through advice from expert Progress Review Groups (PRGs) who work with us to evaluate the state of the science for specific types of cancer or groups of related cancers, identify research gaps and resource needs, and develop recommendations for future priorities. NCI's planning and evaluation process for disease-specific research involves three distinct phases: developing recommendations through the PRGs, planning for and implementing those recommendations with advice from internal implementation working groups, and reporting on progress. This comprehensive and integrated approach to planning helps us demonstrate our progress and the wise use of resources to the scientific community and the public. Through these and other crosscutting efforts, NCI establishes a framework for accountability that is in keeping with the President's Management Agenda and the Congressionally mandated Government Performance and Results Act.

Developing Recommendations

Progress Review Groups (PRGs) are panels of 20 to 30 prominent members of the scientific, medical, private sector, and advocacy communities who are selected to assess the state of the science and recommend future research-related priorities for one type of cancer or a group of closely related cancers. The deliberations of each PRG are informed by a larger group of more than 100 leaders from diverse disciplines and the advocacy community who assemble for a Roundtable Meeting to discuss their understanding of the disease, barriers to progress, and key research and resource priorities for the next five years. PRGs use the input from these Roundtable groups to develop comprehensive and widely distributed reports and recommendations for national research agendas.[1]

For example, recently assembled PRGs have identified some specific initiatives they believe are needed to speed research progress.

- The **Gynecologic Cancers PRG** has identified a need to develop a virtual shared specimen resource that will improve timely access to high quality tissue and body fluid samples and enable gynecologic cancer researchers to exploit emerging genomics, proteomics, and informatics technologies. This critical tool would support the discovery of new and urgently needed early detection methods and new prevention and treatment targets.
- The **Lung Cancer PRG** believes faster progress against the difficult problem of lung cancer will be achieved with scientifically integrated, interdisciplinary, multi-institutional consortia organized

[1] prg.cancer.gov

around the disease, rather than around scientific disciplines. Among its other top recommendations, this PRG has underscored the need for continued research on the genetic, social, and biobehavioral aspects of tobacco control and the need to better elucidate the contributions of injury, inflammation, and infection on lung cancer development.

- The **Kidney and Bladder Cancers PRG** has identified and prioritized research questions across the full spectrum of fundamental research, intervention development, and delivery that will advance progress against these cancers over the next five years. One priority area identified by this group focuses attention on our need to better understand the tumor microenvironment, which likely plays an important role in tumor development and growth in bladder and kidney cancers. Most studies to date have examined only the characteristics of the cancer cells. Expanding the scope of research to include analysis of interactions between the cancer cell and its immediate surroundings and cancer-associated changes in the tumor microenvironment will help researchers to understand the role of cellular communication in tumor development and maintenance. This recommendation aligns with NCI's new thrust to explore how the interaction between the cancer cell and its microenvironment enables and even promotes tumor growth.[2]

A number of common themes have emerged across PRG recommendations that parallel priority initiatives identified in this document. For example, the following were emphasized in more than one PRG recommendation and are closely tied to the capacity building initiatives described on pages 26-45 for supporting research collaborations or development of and access to research resources.

- Cross-disciplinary collaborations such as additional Specialized Programs of Research Excellence (SPOREs) and consortia focused on disease-specific research

[2] See pages 55-59 for NCI's future plans for research on the tumor microenvironment.

Planning National Agendas for Disease-Specific Research: The Progress Review Group (PRG) Process

Recommendation

- NCI leadership appoints PRG co-chairs.
- PRG co-chairs identify & invite PRG members.
- PRG members plan roundtable.
- Roundtable meets & develops recommendations.
- PRG members prepare report & recommendations.
- PRG co-chairs present recommendations to Advisory Committee to the Director.

Implementation

- NCI establishes Working Group of internal experts.
- NCI maps its initiatives & projects to PRG recommendations.
- NCI prepares proposed response to recommendations.
- NCI and PRG hold response meeting.
- NCI prepares & promotes disease-specific strategic plan.

Reporting

- NCI collects progress data.
- NCI develops a progress report.
- NCI & PRG discuss progress.
- NCI revises & promotes disease-specific strategic plan.

In the recommendation phase:
Stomach & Esophageal Cancers

In the implementation phase:
Colorectal Cancers
Brain Tumors
Pancreatic Cancer
Leukemia, Lymphoma, & Myeloma
Lung Cancer
Gynecologic Cancers
Kidney & Bladder Cancers

In the reporting phase:
Breast Cancer
Prostate Cancer

- Enhanced bioinformatics to enable better researcher access to data and analytic tools
- Training on emerging technical developments and career development opportunities related to specific types of cancer, to attract new investigators
- More extensive and fully documented tissue resources
- Preclinical models that more faithfully reflect the behavior of specific tumors in humans

Other recommendations may be addressed through our priority initiatives described on pages 48-92 for supporting research on genes and the environment, signatures of the cancer cell and its microenvironment, molecular targets, cancer imaging, survivorship, and cancer communications.

- Discovery of genetic and environmental factors and interactions that lead to cancer
- Definition of molecular pathways and cellular interactions involved in cancer initiation, progression, and metastasis
- Molecular profiling for the detection of precancerous conditions and early cancers and for monitoring treatment response
- Development and testing of molecular targeted therapy
- Improved imaging for early detection, guided therapy, and real time monitoring of treatment response
- Treatment side effect and quality of life outcomes studies, including establishing registries and cohorts for study
- Education of medical providers and patients about cancer risk, prevention, detection, treatment, follow-up, and end-of-life care

NCI Programs Support Disease-Specific Research

A number of NCI's existing programs support research focused on specific types of cancer.

- Specialized Programs of Research Excellence (SPOREs) have proven to be highly effective channels for disease-specific translational research. The scope of the SPOREs is expanding to establish research hubs for additional cancers so that by the end of Fiscal Year 2002, 40 disease-specific SPOREs will be supported, with further expansions planned. Much of this expansion has been in response to PRG recommendations. Increasingly, SPOREs are partnering with Cancer Centers and NCI-sponsored research networks and consortia to build synergism and share resources to speed progress against specific cancers. Current SPOREs exist for brain, breast, gastrointestinal, genitourinary, head and neck, lung, ovarian, pancreatic, prostate, and skin cancer sites as well as for lymphoma. Future SPOREs will be established for gynecological, leukemia, and myeloma cancers. (See pages 8, 10, 11, and 30 to learn about specific research activities taking place at SPOREs).[3]
- Early Detection Research Network (EDRN) participants develop, evaluate, and validate markers for earlier cancer detection and risk assessment. The Network includes academic and private collaborations and resources for basic, translational, and clinical research. EDRN collaborative groups include those focused on breast, gynecologic, gastrointestinal, lung and upper aerodigestive tract, prostate, and urologic cancers.[4]
- NCI's Innovative Molecular Analysis Technologies (IMAT) program focuses on developing and applying technologies that identify the expression of genes and gene products, the function of major cellular communication pathways involved in cancer, the role of infectious agents in specific cancers, and the significance of other molecular alterations that distinguish normal cells from cancerous ones. (See page 58 for additional information).[5]
- The Mouse Models of Human Cancers Consortium (MMHCC) develops new preclinical models that will enable investigators to better understand specific human cancers and predict the effects of promising therapies. New models continue to be developed for sarcomas and for lung, prostate, mammary, skin, cervical, ovarian, nervous system, blood system, and gastrointestinal cancers. The MMHCC fosters collaboration in these efforts with industry partners and other research institutions.[6]

[3] spores.nci.nih.gov
[4] cancer.gov/prevention/cbrg/edrn
[5] otir.nci.nih.gov/tech/imat
[6] emice.nci.nih.gov

Implementing Strategies to Address PRG Recommendations

Formal strategic plans that respond to PRG recommendations are now being developed under the leadership of disease-specific working groups at NCI. The **Brain Tumor Working Group** proposed the application of new concepts in developmental neurosciences to understand the unique organ-specific biological mechanisms of gliomas in both pediatric and adult patients. The **Leukemia, Lymphoma, and Myeloma Working Group** suggested convening a meeting of leaders from academia, industry, the advocacy community, and government to examine models for establishing public-private partnerships for drug discovery. This could lead to a concept for the funding of planning grants and eventually drug development centers. The **Pancreatic Cancer Working Group** encouraged the funding and training of new investigators, imperative in advancing research on pancreatic cancer.

NCI does everything in its power to expedite progress against all types of cancer. We implement as many of the proposed initiatives in the disease-specific strategic plans as possible, and encourage and enable other organizations to take leading roles on those initiatives where additional collaboration is needed. PRG recommendations are implemented through ongoing NCI initiatives, new or expanded research programs, infrastructure support, partnerships, or a combination of these approaches. Our ability to implement any new initiative is dependent on (1) determining that the initiative is vital, feasible, and sound, (2) availability of funds, and (3) receipt of high quality applications or proposals.

Stalking a Silent Killer — Pancreatic Cancer

Pancreatic cancer is often called a "silent" cancer because it has no clear symptoms until it is advanced. This malignancy metastasizes early, with many tumors as small as 1 or 2 centimeters in diameter spreading beyond the pancreas, and it is resistant to both chemotherapy and radiation treatment. Most patients live six months or less after diagnosis. In 2002, approximately 30,300 new cases will be diagnosed. Experts estimate that 29,700 people will die from this disease in the same time period. Finding better ways to detect, diagnose, and treat pancreatic cancer is absolutely critical.

Researchers are pursuing a number of avenues in search of answers about pancreatic cancer:

- Old age, cigarette smoking, genetic history, chronic pancreatitis, and diabetes are established risk factors for pancreatic cancer. A recent study indicates that obesity increases susceptibility. People who have first degree relatives who have had the disease have a threefold higher risk compared with the general population. Researchers are now trying to learn more about other suspected and corollary risk factors such as chemical exposures and diet in hope of developing effective preventive measures.
- One important avenue of research is to find genes or gene products that influence the tumor's development or progression and could serve as early detection or diagnostic indicators, or targets for better therapies. Research is uncovering a growing number of such genes.
- Several hereditary syndromes and their related genes (such as *p16, BRCA2,*[7] *STK11/LKB1, hMSH2, hMLH1, PRSS1*) have been identified, but these probably account for no more than 5-10 percent of cases.
- Known non-hereditary genetic alterations include activation of the *K-ras* cancer gene, inactivation of a number of tumor suppressing and DNA repair genes, and overexpression of several growth factors and receptors.
- Researchers in the United States and abroad are looking for genes that are influenced by environmental exposures. For example, a recent NCI-funded study demonstrated that a specific deletion in the *GSTT1* gene combined with heavy smoking increased pancreatic cancer risk significantly among Caucasian study participants, with the effect greater in women than in men.

NCI's Pancreatic Cancer Progress Review Group emphasized in its 2001 report[8] that insufficient research funding and the limited number of researchers dedicated to studying the disease have hampered progress against this silent killer. NCI is taking specific steps to help increase the level of research on this highly fatal disease and to encourage researchers to commit to improving care for patients and those at risk for pancreatic cancer.

[7] See page 10 for more information.
[8] prg.cancer.gov/pancreatic/finalreport

Reporting on Progress

We close our accountability feedback loop by providing details to the community on actions we have taken to address PRG recommendations. Recognizing that some actions take longer to demonstrate results, NCI monitors implementation and collects progress data for several years and then prepares a progress report. This report is shared with a reassembled PRG. Based on NCI's assessment of progress and PRG input, implementation strategies are revised, retired, or added as needed, and NCI continues to monitor progress.

By 2003 we will publish progress reports for prostate cancer and breast cancer, in follow-on to the first two PRG reports issued in 1998. NCI will also complete an evaluation of the PRG process itself before the end of this year. The chart on page 19 indicates the current status of reports and plans related to the PRGs established to date.

How We Measure Progress

- Disease trends: decreased incidence, earlier stage of diagnosis, longer survival time, improved quality of life, lower mortality rate
- New FDA-approved interventions: new prevention & treatment agents & drugs, improved diagnostic & treatment technologies
- Ongoing & new clinical trials
- Advances in scientific knowledge: reports of research findings, peer-reviewed publications
- NCI-supported research projects

Targeting a Tumor on the Rise — Kidney Cancer

The incidence of kidney cancer has been increasing about two percent per year for the past several decades. For African Americans, it is rising more rapidly than any other cancer — about four percent per year. Kidney cancer, including tumors of the main part of the kidney and the lower renal pelvis, is now diagnosed in nearly 32,000 people each year in the United States. About 200,000 people are living with kidney cancer. Mortality from the disease is also high and rising, with an estimated 11,600 deaths expected in 2002.

Four main types of kidney cancer have been identified. Clear cell renal tumors are the most common type, accounting for about 75 percent of cases. The reasons for the increase in incidence are not fully understood. Smoking is the most well established risk factor. Obesity, hypertension, occupational exposures, and heavy, long-term use of the pain medication phenacetin have also been linked to greater risk. A small percentage of kidney cancers are hereditary.

More than 40 percent of kidney cancers are not diagnosed until advanced stages. Five-year survival of patients who present with advanced kidney cancer is nine percent. By contrast, approximately 90 percent of patients diagnosed with Stage I disease survive at least five years. Scientists are actively exploring the growing field of proteomics to identify growth factors and other circulating proteins that may be indicators of disease and that can serve as biomarkers for early detection.

Currently, for localized kidney cancer, surgery is the only effective treatment. Minimally invasive and kidney-sparing surgical techniques are becoming more widely used. For metastatic kidney cancer, Interleukin-2 (IL-2) is the only approved treatment. Though highly toxic, IL-2 cures about 10 percent of patients. Scientists are investigating several important molecular pathways as potential targets for less toxic treatments. For example, anti-angiogenesis agents may prove beneficial against clear cell renal tumors. In a recent Phase II clinical trial, high doses of the antibody bevacizumab slowed tumor growth considerably in patients with metastatic kidney cancer.[9] More than 20 other trials are now underway to evaluate this antibody as a treatment for other types of cancer.

In 2001, NCI convened a Kidney and Bladder Cancers Progress Review Group to assess our understanding and treatment of these diseases and identify research priorities and infrastructure needs for accelerating progress over the next 5 to 10 years. An NCI implementation planning group has been convened to analyze the recommendations[10] and determine how the recommendations can be implemented.

[9] See page 10 for more information.
[10] prg.cancer.gov/kidney

A couple of years ago, I started having frequent indigestion and heartburn. I've always loved spicy food, and I figured, at my age, my stomach was finally starting to complain about it. But I was taking more and more antacids, so I finally mentioned it to my doctor. After talking to him, I was glad I did.

Esophageal Cancer

This year, more than 13,000 people will be diagnosed with esophageal cancer and an estimated 12,600 will die of this disease. It will strike three to five times more men than women. Of the two types of esophageal cancer, squamous cell tumors have been historically more prevalent. However, for reasons that are not well understood, rates of adenocarcinomas of the esophagus are rising at an alarming rate.

The rise in adenocarcinoma has been extraordinarily steep among white men, surpassing the incidence of squamous cell tumors in this population.

In contrast, African American men, who have the highest overall esophageal cancer rates of any population in the United States, develop squamous cell tumors more often than adenocarcinomas. Moreover, they tend to develop the disease earlier than other groups and have poorer survival rates. Though still high, squamous cell esophageal cancer rates are falling among African American men, possibly due to lower smoking rates since the 1960s.

Barrett's esophagus is the most significant precursor for **esophageal adenocarcinoma**. It occurs when normal squamous epithelial cells that line the lower esophagus are replaced by columnar epithelial cells such as those normally found in the stomach.

The condition is believed to be linked to the chronic reflux (backing up) of stomach acid into the esophagus, and obesity has been shown to increase the risk. Many cases of Barrett's esophagus are preventable since the condition is easy to detect with a relatively simple test. But patients may consider even chronic heartburn too trivial to mention to their doctors, and often physicians fail to ask about the problem. The most effective screening and treatment approaches for Barrett's esophagus remain in question.

Studies suggest that a few risk factors account for virtually all of the **squamous cell esophageal cancers** in the men studied and for 99 percent of the excess occurence in African American men.

- Major contributors to the development of squamous cell esophageal cancer are tobacco use and heavy alcohol consumption, particularly in combination.
- A recent NCI study reports that low income and infrequent consumption of fruits and vegetables also account for susceptibility to this disease.

For all esophageal cancers together, the median age at diagnosis for males is 67 years. For females, it is 73 years. Of these, 66 percent will be in the age group 65 years and older.

In 2002, NCI convened a Stomach and Esophageal Cancer Progress Review Group to assess the current state of knowledge about esophageal cancers and identify the research and resources needed to answer the many important questions about both forms of this deadly disease. Go to **prg.cancer.gov/stomach** to see the report.

Planning and Priority Setting for Cancer Research

NCI plans and sets priorities to ensure that we are responsive to new discoveries and opportunities, while making the best use of our resources. NCI staff work together and with public and private partners from the scientific, medical, and advocacy communities to determine what is needed and how best to move the science forward. We plan for research that can address critical unanswered questions covering the many types of cancer and the various populations that experience them. We strive to integrate basic, behavioral, population, and applied research through translational activities and strive to identify new opportunities, as well as gaps and barriers to progress, that help us create new programs and improve existing ones. We keep our research portfolio balanced and our support structure strong through program assessment.

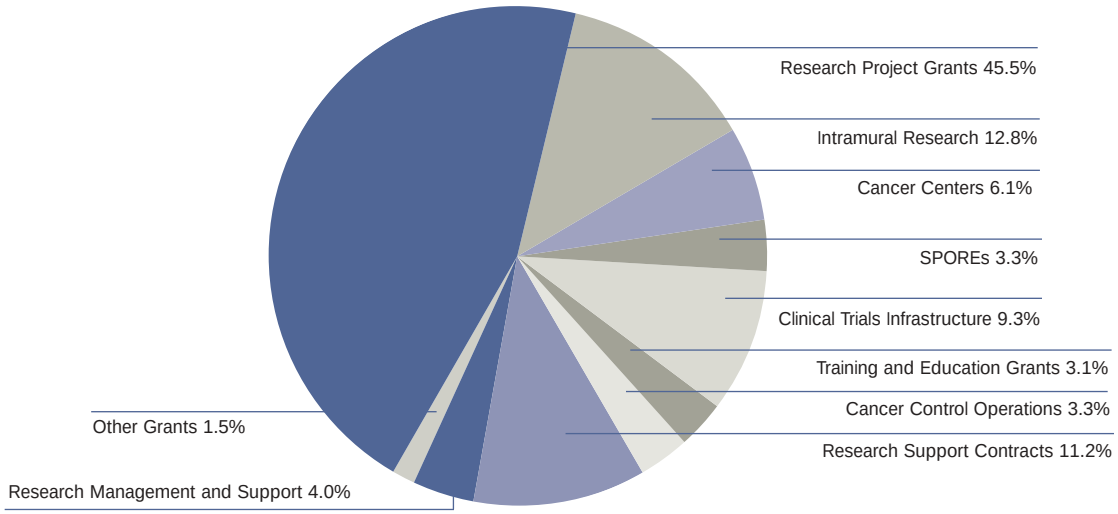
Over the past several years, the National Cancer Institute has identified and fostered the development of several broad priority areas that serve as the framework for our annual strategic planning and budget development. **NCI Challenges** are areas of emphasis that focus investment on improving the resources and mechanisms available to support research, furthering the preparation of the people needed to conduct research, enhancing access to research information and technology, and maximizing the sharing of discovery and collaboration among researchers and clinicians. **Extraordinary Opportunities for Investment** are areas of discovery that build upon the most important recent developments in knowledge and technology and hold promise for making significant progress against all cancers. They are developed with formal input from members of the research community, advisory groups, and advocacy organizations. These priority areas are the "breaking news," the emergent fields of cancer research. Some of these Challenge and Extraordinary Opportunity areas also address major public health needs or concerns that have potential to affect large numbers of people at risk for or affected by cancer. Pursuing these priorities will enhance our understanding of the clinical outcomes resulting from cancer interventions; improve our ability to apply the best available cancer-related knowledge, technology, and interventions in clinical practice and public health; and ensure that we do all that we can to reduce health disparities in cancer incidence and outcomes.

Thus, the framework for our Fiscal Year 2004 Plan and Budget is comprised of three major components to complement our core budget for continuing research and support activities. Each of these includes cross-cutting and focused research on specific types of cancer as described in the **National Agendas for Disease-Specific Research** developed in consultation with Progress Review Groups.

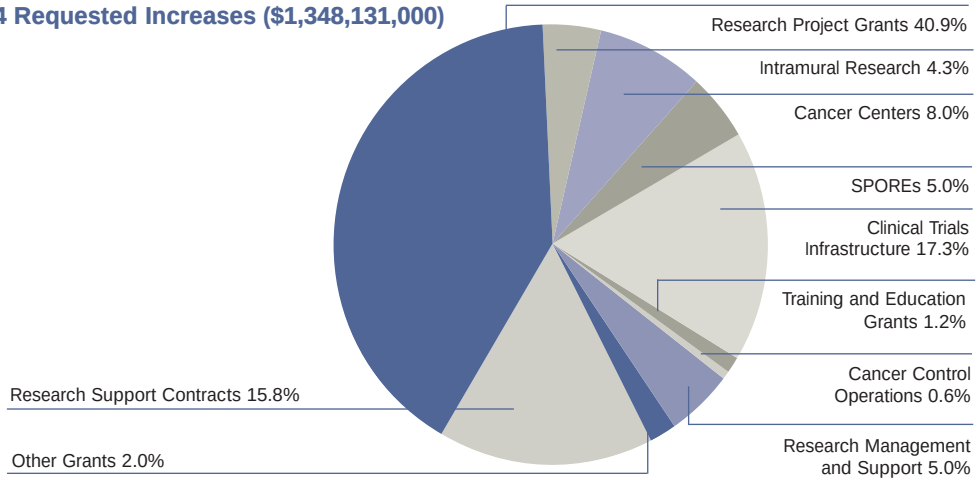
- **Building the Nation's Cancer Research Capacity** requires increased support to four NCI Challenge areas:
  - — Enhancing Investigator-Initiated Research
  - — Expanding the Capacity of Centers Networks, and Consortia
  - — National Clinical Trials Program in Treatment and Prevention
  - — Developing Bioinformatics for Cancer Research.
- **Advancing Discovery and Its Application** means further pursuing "Extraordinary Opportunities for Investment" in:
  - — Genes and the Environment
  - — Signatures of the Cancer Cell and Its Microenvironment
  - — Molecular Targets for Prevention and Treatment
  - — Cancer Imaging and Molecular Sensing
  - — Cancer Communications
- **Addressing Areas of Public Health Emphasis** requires increased support for:
  - — The Challenge for Improving the Quality of Cancer Care
  - — The Challenge for Reducing Cancer-Related Health Disparities
  - — A new Extraordinary Opportunity in Cancer Survivorship research
  - — An Extraordinary Opportunity for Research on Tobacco and Tobacco-Related Cancers

The Nation's Investment in Cancer Research

Distribution of 2004 Budget Request ($5,986,000,000)



Distribution of 2004 Requested Increases ($1,348,131,000)



Research Project Grants

Funding for extramural research, primarily through investigator-initiated Research Project Grants (RPGs), comprises the largest part of the NCI core budget. Increases through the NCI Challenge and Extraordinary Opportunity initiatives contribute to the expansion of research supported through RPGs. NCI funds about 4,500 RPGs each year to nearly 600 institutions across the United States at an average cost of approximately $400,000 per grant. If fully supported, our budget request for Fiscal Year 2004 would add $523 million to the funds available to support investigator-initiated research.

Intramural Research

NCI intramural research focuses on projects conducted by some 400 researchers located on the NIH campus. These researchers build upon the proximity between their research laboratories and the NIH Clinical Center and the synergism among NIH Institutes to support the rapid translation of basic laboratory research to the clinic and to maintain a special focus on long-term epidemiologic and genetics studies.

Cancer Centers and Special Programs of Research Excellence (SPOREs)

Sixty NCI-supported Cancer Centers serve as hubs for cutting-edge research, high quality cancer care, and outreach and education for healthcare providers and patients. Centers of Excellence like the SPOREs use flexible funding to pursue questions related to specific forms of cancer and to move disease-specific research quickly from the laboratory to the patient. Funding increases will allow NCI to broaden the number and range of activities at Cancer Centers and SPOREs.

NCI Budget Request for 2004

(dollars in thousands)	2002 Operating Budget	2003 President's Budget	2004 Budget Request Increases	2004 Budget Request Total
Research Project Grants (RPGs)				
Ongoing	$1,450,697	$1,557,941	$ 89,160	$1,647,101
New and Renewal	456,000	516,711	434,625	951,336
Subtotal	1,906,697	2,074,652	523,785	2,598,436
Small Business Innovation Research	85,995	100,294	26,995	127,289
Total RPGs	1,992,692	2,174,946	550,779	2,725,725
Intramural Research	630,036	706,258	58,132	764,390
Cancer Centers	227,831	254,246	107,937	362,183
Specialized Programs of Research Excellence (SPOREs)	108,921	127,696	67,725	195,420
Clinical Trials Infrastructure				
Cooperative Clinical Research	161,711	198,060	157,628	355,688
Community Clinical Oncology Program (CCOPs)	105,522	123,187	76,108	199,295
Total Clinical Trials Infrastructure	267,233	321,247	233,736	554,983
Training and Education Grants				
National Research Service Awards	64,083	73,289	4,926	78,215
Research Career Program	54,177	65,327	5,500	70,827
Cancer Education Program	27,170	25,456	3,942	29,398
Minority Biomedical Research Support	3,980	4,522	1,167	5,689
Total Training and Education Grants	149,410	168,594	15,535	184,129
Cancer Control Operations	154,306	188,429	7,722	196,151
Research Support Contracts	425,440	457,941	212,644	670,585
Research Management and Support	150,757	173,200	66,758	239,958
Other Grants	60,371	65,313	27,163	92,475
Total NCI	4,166,997	4,637,869	1,348,131	5,986,000
*Cancer Control included above***	*491,645*	*546,792*	*308,821*	*855,613*

Clinical Trials Infrastructure

NCI supports clinical trials carried out by approximately 10,000 investigators at some 1,700 U.S. hospitals and Cancer Centers each year. Nearly 1,500 trials are conducted annually, assisting over 200,000 patients. These trials make possible the testing of targeted agents that hold promise for more effective, less invasive, cancer prevention and treatment and technologies that can be used for better detection and diagnosis. About three-quarters of this funding is for treatment trials and the other quarter supports prevention and screening trials.

Training and Education Grants

NCI funds approximately 170 institutions and 2,000 individuals each year through extramural cancer research training programs to prepare the next generation of scientists and clinicians to use new technologies and work effectively in interdisciplinary, collaborative research environments. Increased funding will be used to enhance these programs and to support the participation and growth of scientists within underserved populations.

Cancer Control**

NCI's cancer control operational funds along with numerous grants and contracts included throughout the budget are used to support research, communication, and other activities focused on ways to reduce cancer risk, incidence, morbidity, and mortality and improve the quality of life for all cancer patients. Increases will be used to support research on tobacco and tobacco-related cancers, reducing cancer-related health disparities, improving the quality of cancer care, cancer survivorship, cancer communications, and a host of other information dissemination activities.

Requested Increases for Fiscal Year 2004*

(dollars in thousands)		Core Increase	Capacity Building Increase	Discovery and Application Increase	Public Health Emphasis Increase	Total Increases
Research Project Grants (RPGs)						
Ongoing		$ 89,160	$ -	$ -	$ -	$ 89,160
New and Renewal		35,988	99,737	169,100	129,800	434,625
	Subtotal	125,148	99,737	169,100	129,800	523,785
Small Business Innovation Research		20,995	-	6,000	-	26,995
	Total RPGs	146,142	99,737	175,100	129,800	550,779
Intramural Research		26,132	27,000	5,000	-	58,132
Cancer Centers		24,907	72,830	8,200	2,000	107,937
Specialized Programs of Research Excellence (SPOREs)		32,725	30,500	4,500	-	67,725
Clinical Trials Infrastructure						
Cooperative Clinical Research		7,328	132,900	7,500	9,900	157,628
Community Clinical Oncology Program (CCOPs)		4,558	71,550	-	-	76,108
	Subtotal	11,886	204,450	7,500	9,900	233,736
Training and Education Grants						
National Research Service Awards		4,926	-	-	-	4,926
Research Career Program		2,500	-	-	3,000	5,500
Cancer Education Program		942	-	1,000	2,000	3,942
Minority Biomedical Research Support		1,167	-	-	-	1,167
	Subtotal	9,535	-	1,000	5,000	15,535
Cancer Control Operations		6,972	-	-	750	7,722
Research Support Contracts		16,944	103,850	44,450	47,400	212,644
Research Management and Support		6,408	39,150	16,700	4,500	66,758
Other Grants		12,363	-	3,800	11,000	27,163
	Total NCI	294,014	577,517	266,250	210,350	1,348,131

*Increases over the 2003 President's Budget

Research Support Contracts
Research support contracts are used to support program efforts across the Institute. Areas that utilize contracts are diverse and include such areas as drug development, cancer control research, information dissemination, and support to epidemiological research.

Research Management and Support
Research management and support budgets are used for the critical technical and administrative services required for NCI to carry out its work. They include central administrative functions, overall program direction, grant and contract review and administration, personnel, program coordination, and financial management.

Other Grants
Other grants support partnerships and shared resources and scientific evaluation, workshops and conferences.

The ever-changing technological and scientific landscape requires that we constantly re-examine how we interact as scientists to conduct our research and what resources are necessary to yield results.
— Andrew C. von Eschenbach, M.D.

Building the Nation's Cancer Research Capacity

The challenge before NCI is to build and continually enhance a research system that will allow and encourage the scientific community to share and apply new discoveries and emerging technologies. We need new funding arrangements that will promote and reward innovative thinking; speed cross fertilization of ideas among disparate scientific disciplines; facilitate collaborations among government, academia, and industry; and bring advances in cancer care to all populations. And we need to foster and coordinate efforts that would be too large for the individual investigator by promoting team endeavors, and by encouraging scientific integration without inhibiting individual creativity.

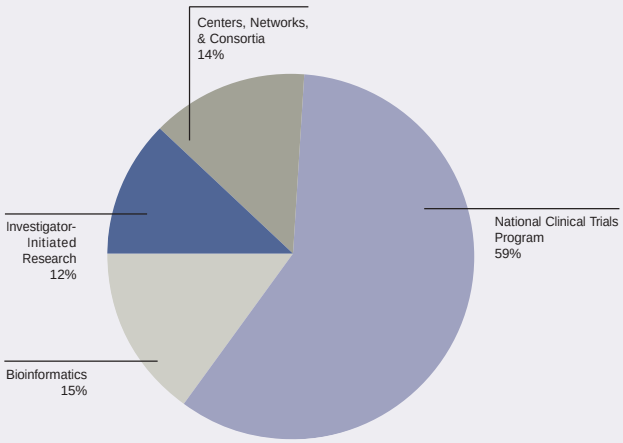
Advances in working with specific types of cancer may emerge from non-specific cancer knowledge and resources, and new knowledge in one type of cancer often has implications for better understanding other cancers. To make progress for as many cancers as possible, we need to:

- Guide, support, leverage, and build the work of the individual investigator along with that of our NCI-supported Cancer Centers, networks, and consortia.
- Maximize caregiver and patient access to clinical trials for prevention, diagnostic, and therapeutic interventions.
- Train top researchers in oncology and arm them with the finest technologies and tools available.
- Build and sustain the interdisciplinary connections so vital to 21st century science.

We will continue to build the Nation's cancer research capacity for the future by *Enhancing Investigator-Initiated Research*, *Expanding the Capacity of Centers, Networks, and Consortia*, maximizing the impact of our *National Clinical Trials Program in Treatment and Prevention*, and *Developing Bioinformatics for Cancer Research*.

FY 2004 Increase Request for Capacity Building
(dollars in thousands)

Investigator-Initiated Research	$ 69,887
Centers, Networks, & Consortia	$ 79,530
National Clinical Trials Program	$340,100
Bioinformatics	$ 88,000
Total	**$577,517**



GOAL

Accelerate discoveries and their application by expanding and facilitating researcher access to resources and new technologies.

Enhancing Investigator-Initiated Research

The Challenge

Investigator-initiated research — research independently conceived and developed by scientists — has always been the primary means by which biomedical research is funded and conducted. Driven by the synergism at medical schools, hospitals, universities, and research centers, these investigators ask the critical questions, explore the options, develop and test innovative technology, and make the discoveries that lead to better cancer science and its application. Investigator-initiated research is also the principal means by which NCI supports efforts to address high-priority goals, such as those identified by the Progress Review Groups.

Recent advances, highlighted by the completed sequencing of the human genome, new technologies for identifying molecular targets within cancer cells, and methods for discovering and analyzing promising drugs aimed at each cancer-causing pathway, have outfitted scientists with a wider arsenal of approaches and technologies for research than ever before. The exploration of what we can learn from analyzing all of the genes altered in a cancer cell is expanding rapidly. Even as this is happening, investigators are developing powerful methods to analyze the vastly more complex array of proteins made in the cell. This offers a more direct route to identify targets for new drugs. However, to take advantage of these advances, researchers often require additional resources, in the form of new research tools and equipment, collaborators from different disciplines, or special support for translational research. Providing these resources is part of NCI's challenge in the area of investigator-initiated research.

NCI has seen an enormous increase in the need for funding to allow scientists to fully exploit new technologies and approaches to conducting research. In Fiscal Year 2002, for example, the number of applications submitted to NCI increased by 6 percent, and the cost of research projects supported by NCI was nearly 14 percent higher than the year before. This cost increase reflects a larger number of total active awards as well as modest growth in average cost. While we expect this trend to moderate, we must balance the growing number of research opportunities with the rising costs of research. Though reviewer assessments of research applications consistently identify the top 35 to 40 percent of grants as highly meritorious, the proportion actually funded (the success rate) has averaged 29 percent in recent years. NCI has maintained this success rate by carefully reviewing individually approved grant applications for programmatic changes, the effect of which is, on average, a reduction of 10 percent to the cost of a grant. As research opportunities increase, we must, in addition to leveraging our Federal dollars, ask researchers to complement this funding from other sources as much as possible.

The next generation must choose to enter cancer research because of opportunities for discovery with the potential to change our world. A sufficient infusion of resources and funding into investigator-initiated research will help to ensure that students considering a career in science, as well as current researchers, will perceive cancer research as an appealing and rewarding profession.

Progress Toward Meeting the Challenge

The NCI has sought to support and foster investigator-initiated research through a variety of policy decisions and flexible funding options.

Enhancing Investigator-Initiated Research

G O A L

Accelerate discoveries and their application by expanding and facilitating researcher access to resources and new technologies.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Accelerate the pace of discovery through increased funding for and greater numbers of competing research grants.

- Support research projects to move toward funding at the full levels recommended by peer reviewers.
- Fund, at a minimum, 35 percent of competing applications — those with (1) the highest scientific merit, (2) a less certain probability of success but potential to yield greater reward if they do succeed, (3) unconventional approaches but unique promise, (4) a focus on areas of extraordinary need in specific fields of investigation or model systems, and/or (5) the involvement of new investigators.

2. Encourage investigators to commit to careers in cancer research and to propose more innovative and higher reward projects.

- Continue to allocate the first 80 to 90 percent of available funds for research project grants through the well-established peer review selection process while ensuring that proposals from new investigators are also funded at a rate comparable to those of more established investigators, utilizing exceptions as necessary.
- Through a special administrative evaluation process, fund particularly innovative and potentially high reward projects.

3. Facilitate rapid movement from discovery to application by using established mechanisms and creating novel special awards to encourage transdisciplinary and collaborative research.

- Expand supplemental funding for grants that promote new interdisciplinary collaborations for bringing together basic, clinical, and population scientists, such as those

Balancing Investigator-Initiated Research Projects and Large Initiatives

There's no substitute for individual insight and creativity. That's why the traditional research project grant (R01) remains the heart of the NCI portfolio of investigator-initiated research and remains our number one priority. The Human Genome Project exists at the other end of the spectrum — a large consortium of investigators and an initiative that produced massive amounts of uniquely valuable data, generated using expensive, high technology instrumentation. We now appreciate how necessary these large endeavors are, but the difference in scale threatens to create the scientific equivalent of the "digital divide." The challenge is to balance the flow of resources to ensure that the individuals with the best ideas continue to have access to the resources they need.

In recent years, NCI has expanded funding for a variety of large-scale initiatives to capitalize on the insights and tools derived from genetics research, proteomics, functional imaging, nanoscience, laboratory and clinical models, and targeted drug discovery and development. The success of such large-scale approaches,

fostered by NCI's Activities to Promote Research Collaborations Program.

- Expand researcher access to central resources such as databases, tissue banks, and animal models using funding supplements; centers, networks, and consortia; and cooperative resource programs.
- Expand researcher access to technologies that promote interdisciplinary research and collaborations and to the expertise needed to move discoveries to application.
- Develop and make available information technology tools to foster and enhance interdisciplinary communication and collaboration.
- Expand the funding for collaborative research awards such as program project grants and cooperative agreements for consortia that facilitate translational research.
- Expand the use of exploratory grants to encourage more patient- and population-based research.

4. Use regular and special award mechanisms to encourage investigation in priority areas identified by advisory committees, NCI staff, Progress Review Groups, and other groups. Leverage resources for these efforts through collaborative initiatives.

- Monitor investigator-initiated research to assess whether these projects alone are meeting programmatic objectives, such as those identified in specific disease areas.
- Set aside 10 to 15 percent of funds for Requests for Applications in specifically targeted areas of need.
- Support Program Announcements and investigator-initiated projects that target identified gaps and/or emerging opportunities (e.g., as identified by the Progress Review Groups and other priority setting and strategic planning activities).
- Enhance coordination within and among initiatives, and increase management and support commensurate with the growth of the portfolio.
- Use supplemental awards to encourage outreach to establish public-private partnerships and to leverage current NCI funded activities with new, complementary non-NCI sources of support.

Management and Support		**$ 2.00 M**
	Total	**$ 69.89 M**

however, increasingly will require individual investigators to prosper by working in conjunction with others to have access to specialized facilities needed to compete. Therefore if individual grants are to continue to lead the way in innovation, NCI infrastructure models must have the capability of marrying individual expertise and imagination to state-of-the-art resources.

To assure such balance is maintained, NCI staff work to provide broad access to NCI-funded resources, where possible, and to ensure that individual researchers are aware of all the resources available to them. But other related initiatives that provide infrastructure assets such as large-scale instrumentation and bioinformatics support are also integral to maintaining investigator-initiated research. Reasonable growth in average costs, flexible funding options, and full funding for R01s are essential to maintaining access to such technologies to ensure that the next generation of creative investigators working on cancer continues to flourish in independent settings.

Identifying and Supporting High Priority Research

NCI takes extra steps to identify and support high priority research by:

- Seeking out and supporting compelling research proposals with exceptions funding, particularly those suggesting dramatically new or unconventional approaches to understanding cancer.
- Giving special consideration to proposals responsive to high-priority research areas identified by NCI advisory groups, to NCI Program Announcements of priority research areas, and to recommendations from Progress Review Groups for research related to specific cancers.

We are also exploring better ways to define and promote the exploration of uncharted areas and to give them heightened consideration when reviewing grant applications.

Maximizing the Ability to Start New Projects and Collaborations

NCI maximizes the pace of discovery by providing a broad range of flexible funding options and promoting collaborations and resource sharing wherever possible by:

- Providing opportunities for collaborative study through awards such as program project grants (P01s) and cooperative agreements, in addition to the traditional research project grants (R01s) that make up the bulk of NCI's research portfolio.
- Expanding the use of award mechanisms that provide seed funds for promising research. In Fiscal Year 2001, the number of small (R03) and exploratory/developmental (R21, R33) grants awarded increased more than 15 percent over the previous year.
- Making "administrative supplement" funds available to investigators to allow them to take advantage of unanticipated opportunities or to pursue interdisciplinary collaborations. For example, through NCI's Activities to Promote Research Collaborations Program, grantees can apply for funding in support of collaborations to initiate novel research that pursues unforeseen opportunities and to share resources, develop new technologies, or organize cross-disciplinary meetings or workshops.
- Promoting collaborative studies and sharing of resources through innovative networks and consortia. (See pages 32-35.)

Better Understanding the Cell Microenvironment Holds Promise for More Effective Cancer Treatment and Prevention

For many years, scientists have conducted studies of cells by removing them from their natural surroundings, assuming that the proteins, accessory cells, and blood vessels within a cell's immediate surroundings — its microenvironment — provide nourishment and support with little effect on the cell's function. But scientists now know that a cell and its microenvironment have a dynamic and intimate relationship. In the embryo, this relationship ensures that organs develop properly. In the adult, it helps to maintain the stability needed for cell functioning and influences a host of cell activities, such as proliferation and programmed cell death.

The cell-microenvironment relationship also plays an important role in cancer development and progression. When a lone cancer cell arises from multiple changes in its own genes, it does not pose a threat to the body. But when it progresses to a tumor mass comprised of cancer cells and cells from the surrounding environment, it becomes a serious health concern. Researchers have observed that:

- The abundance of growth factors in the microenvironment provides a readily available source of growth-promoting signals to tumor cells.
- The influence between the microenvironment and cancer cells is bi-directional. Scientists must now determine whether neighboring cells lose their natural capacity to suppress cancer cell growth or whether they acquire an attribute that permits tumor growth.
- An enzyme induced in inflammatory cells found in the microenvironment appears to be the elusive "angiogenic switch" that turns on the formation of new blood vessels needed to keep cancer cells alive.

This broadened concept of cancer has taken us from focusing exclusively on the cancer cell to exploring how the interplay between the cancer cell and its immediate environment supports tumor growth. Ultimately, this will enable us to explore the impact of tumor growth on the entire body. Rather than targeting the cancer cell alone, new prevention and treatment approaches will potentially target the features of the microenvironment that allow tumors to develop and progress.
For information on NCI's future plans for research in this area, see pages 55-59.

Increased Investment Strengthens Research Training and Career Development

Rapid developments in the frontiers of molecular biology and translational medicine have broadened the scope of disciplines needed for cancer research and have presented new challenges for training future cancer researchers. In 1998, NCI launched a strategic plan for ensuring a future cadre of well trained scientists prepared to tackle emerging questions in basic, clinical, behavioral, and applied cancer research. Equally important was ensuring a future that included broader participation of minority students and scientists in pursuing careers in cancer research. This strategic plan became the foundation for the goals and objectives outlined in NCI's Challenge Area for Research Training and Career Development, a component of NCI's Plan and Budget proposal since Fiscal Year 1999. NCI is not requesting budget increases in this area for 2004, but we continue to use multiple strategies to ensure a future of talented, diverse, and innovative cancer researchers to meet the needs of the ever changing cancer research environment.

- Career Awards and National Research Service Awards are flexibly administered to meet the various needs of researchers ranging from predoctoral candidates who need mentoring to established scientists who are leaders and resources in their fields.
- The NCI Transition Career Award provides "protected" time to postdoctoral trainees as they transition to independence and to newly autonomous investigators as they start to develop their first independent research programs.
- New Diversified Career Development Awards attract scientists in disciplines not traditionally associated with cancer research but clearly needed for the future.
- Supplemental funding to existing training programs through the Continuing Umbrella of Research Experiences Program and the Comprehensive Minority Biomedical Branch increases the pool of underrepresented minority candidates in the biomedical pipeline from high school through advanced research training.
- Collaborations between Minority-Serving Institutions and NCI-designated Cancer Centers support minority scientists and projects that focus on cancers that disproportionately affect minority populations.
- The career development program through Specialized Programs of Research Excellence supports the recruitment or reorientation of laboratory and clinical scientists to translational research on human cancer.
- Twenty Institutional Clinical Oncology Career Development Programs prepare clinical scientists to design and implement hypothesis-based clinical trials and collaborate with basic scientists.
- The Cancer Education Grant Program is aimed at developing innovative educational approaches to decrease cancer incidence, morbidity, and mortality.
- The Cancer Education and Career Development Program encourages institutions to develop programs dedicated to training investigators at the predoctoral and postdoctoral level in highly interdisciplinary areas such as cancer prevention and control; population sciences; molecular epidemiology, pathology, and pharmacology; and imaging.

NIH supports the development of Web-based data collection to provide information about students and postdoctoral trainees. This information can help to quantify fulfillment of future training requirements. For example, a recent NCI report compares Ph.D. recipients in the behavioral and biomedical sciences, who have received at least nine months of National Research Service Awards support, to their colleagues without this support. Data show that in most respects these award recipients outperform their peers.

For additional information on research training, career development, and educational opportunities available through NCI, go to **cancertraining.nci.nih.gov.**

GOAL

Create and sustain infrastructures that facilitate research collaboration, serve as platforms for technology development, and provide access to the full range of research resources.

Expanding the Capacity of Centers, Networks, and Consortia

The Challenge

Today's cancer researchers cannot excel in an intellectual or administrative vacuum. To maximize innovation, researchers must work effectively in an interdisciplinary environment that allows and encourages them to engage in newly emerging areas of research and technology development and to take full advantage of opportunities to move science forward to benefit patients and the public health. They need sophisticated tools, extensive — and expensive — information resources, and trained associates to make meaningful progress. And they need research infrastructures that promote collaboration in basic, clinical, and population research and among scientists in fields such as physics, computer science, and engineering. Investigators must have access to patients and at-risk populations as well as to tissue banks, new technologies, and state-of-the-art informatics. And we must establish more effective linkages among oncologists, researchers, the pharmaceutical industry, cancer advocates, and policy makers to ensure that the results of discovery and intervention development reach those people who need them.

NCI's challenge is to address these critical needs by continuing to expand the capacity of centers, networks, and consortia to most effectively:

- Build and sustain research infrastructures that encourage and reward multidisciplinary research and scientific collaborations.
- Broaden the geographic distribution and impact of NCI-designated Cancer Centers.
- Improve the access of underserved populations to state-of-the-art research and resources.
- Engage in new areas of research and technology development.
- Make expertise, facilities, clinical practice and public health guidelines, and other resources broadly available to physicians and other caregivers, patients and families, and appropriate health agencies.

Progress Toward Meeting the Challenge

Building and Sustaining Infrastructures for Translational Research

NCI's overarching structure for research supports NCI-designated Cancer Centers, Centers of Research Excellence, research networks and consortia, as well as individual investigators. This framework helps create an environment conducive to complex scientific interactions, provides the resources essential for the research, and encourages the easy exchange of information and ideas. The challenge of the future will be to ensure that our numerous interactive linkages function at peak effectiveness, allowing investigators to seek answers to major questions more efficiently and effectively. Within this structure, there are several levels of interaction. **NCI-designated Cancer Centers** organize and integrate multidisciplinary research across departments and schools within a single institution or consortium of institutions. They provide scientists access to the most advanced technologies and new research opportunities.

These Centers, in turn, have given rise to **Centers of Research Excellence** that bring together interdisciplinary and translational research teams focused on specific diseases, modalities, biologic processes, or scientific areas. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities.

- Specialized Programs of Research Excellence (SPOREs) provide platforms for interaction, collaboration, and intervention development for specific cancers. They serve as highly effective hubs for translational research, moving discoveries among laboratory, clinic, and population research settings. In just 10 short years this program has grown substantially, with 40 SPOREs conducting and facilitating translational research in brain, breast, gastrointestinal, pancreatic, genitourinary,

head and neck, lung, lymphoma, ovarian, prostate, and skin cancers.[1]

- Modeled on the SPORE blueprint, other strategic Centers of Research Excellence include Transdisciplinary Tobacco Use Research Centers, *In Vivo* Cellular and Molecular Imaging Centers, Interdisciplinary Research Teams for Molecular Target Assessment, and Centers of Excellence in Cancer Communications Research. The newest of these are the interdisciplinary Centers for Population Health and Health Disparities.[2]

NCI is working to build better ways for these Centers of Research Excellence to share data, research concepts, and mechanisms for developing interventions. It is through these collaborative efforts that NCI can further leverage its resources and ensure the best stewardship of Federal funding.

NCI-supported **networks and consortia** are also integrated with Cancer Centers and other programs in important ways.

- Special Populations Networks for Cancer Awareness Research and Training build relationships between large research institutions and community based programs to find ways of addressing important questions about the burden of cancer in minority communities.
- Through the NCI Minority Institution/Cancer Center Partnership program, Cancer Centers are developing long-term relationships with the Minority Serving Institutions to increase research, training, and outreach dedicated to reducing the disproportionate cancer incidence and mortality in minority populations. Five of these partnerships have been initiated to date and other collaborative efforts are underway through planning grants.
- The Cancer Genetics Network is a national network of researchers located in NCI-designated Cancer Centers who specialize in the study of inherited predisposition to cancer.
- The Mouse Models of Human Cancers Consortium, a valuable resource for cancer researchers engaged in a variety of basic, translational, clinical, and epidemiological investigations, has components in Cancer Centers. Consortium participants collaborate with investigators in the NCI Director's Challenge program, the SPOREs, and the Early Detection Research Network (EDRN)[3] to evaluate various high-throughput technologies to ensure that compatible technologies are developed for mouse research.
- Further interactions are ongoing among EDRN investigators, SPORE investigators, and other interdisciplinary groups to facilitate the discovery, development, and initial steps in clinical validation of molecular markers and assays that detect early signs of cancer.

Bringing State-of-the-Art Research Results to Cancer Patients

NCI-supported Cancer Centers, networks, and consortia can serve as natural hubs for national leadership in the war against cancer and provide a means for fostering coalitions and partnerships with other cancer funding organizations, professional societies, businesses, industry, communities, and local and state governments.

In the last five years, more than 40 of the 60 Cancer Centers have received the "comprehensive" designation. This includes most medical institutions in the United States with major biomedical research programs. Directors and investigators at these Comprehensive Cancer Centers participate proactively with NCI in outreach activities to more rapidly bring the benefits of research to patients, physicians and other caregivers, and communities, especially to those in under-represented geographic regions of the Nation. NCI is working to facilitate the establishment of regional cancer centers — partnerships between smaller institutions and the large, existing NCI-designated Comprehensive Cancer Centers — to provide patients and populations with much improved access to the newest trials in early detection, prevention, and therapeutic research.

In the summer of 2002, The National Cancer Advisory Board assembled an Ad Hoc working group to establish a blueprint for NCI-designated Cancer Centers and SPOREs. The Ad Hoc group was charged with considering strategies for balancing the breadth and depth of the centers program, maximizing translation of research discoveries, developing objectives of a national cancer agenda focused on reducing the cancer burden, and facilitating partnerships with other governmental, private, philanthropic, and industrial entities. Recommendations from the working group are expected in early 2003.

[1] **spores.nci.nih.gov**
[2] See page 84 for more information.
[3] **cancer.gov/prevention/cbrg/edrn**

Expanding the Capacity of Centers, Networks, and Consortia

G O A L

Create and sustain research infrastructures and collaborations that enable multiple scientific disciplines to address large problems in human cancer that cannot be solved by individual investigators. Promote networks, partnerships, and coalitions that increase the pace of translational research and the rate at which the results of research are translated into clinical practice and public health benefit.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Increase the number and geographic distribution of NCI-designated Cancer Centers. — **$ 6.25 M**

- Designate one new Cancer Center. $1.50 M
- Bring Cancer Center resources and expertise to two regions of the country with large underserved populations by designating two specialized Centers or by direct partnerships between regional institutions and existing Comprehensive Cancer Centers. $2.50 M
- Award two new Cancer Center Planning Grants to institutions in areas of the country not currently served by Cancer Centers. $0.75 M
- Plan a new Cancer Center consortium mechanism in regions of the country in which no single institution has the research strength to become a traditional NCI-designated Cancer Center. $1.50 M

2. Encourage collaborations and partnerships to improve access of minority populations to state-of-the-art clinical and population studies, cancer treatments, technologies, and care. — **$ 6.00 M**

- Continue to support formal partnerships between Cancer Centers and Minority Serving Institutions in the form of two comprehensive partnerships and one planning grant to enhance the research capabilities of the institutions and improve the effectiveness of Cancer Centers in serving minority communities. $5.50 M
- Integrate NCI-designated Cancer Centers and Minority Institution/Cancer Center Partnerships with the NCI Special Populations Networks for Cancer Awareness Research and Training. $0.50 M

3. Expand the capacity of NCI centers, networks, and consortia to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions. — **$51.08 M**

- Provide additional funding to build the clinical research and population research infrastructure of NCI-designated Cancer Centers. Fund databases that conform to NCI's clinical informatics infrastructure; support the development and expansion of population databases and other resources; provide more core staff to conduct innovative translational therapeutic and prevention trials; and strengthen the auditing and data safety and monitoring of human subjects research to conform to Federal regulations. $15.00 M

- Promote and develop matching fund and co-funding partnerships of NCI-designated Cancer Centers with industry and national, private, state, and community organizations, as well as with other cancer funding organizations, to expand the conduct and impact of translational research. $5.00 M
- Encourage NCI-designated Cancer Centers, networks, and consortia to network with each other to integrate best practices, share protocols, and maximize collaborative research opportunities and avoid duplication of resources. $0.50 M
- Build on NCI's Prostate, Lung, Colorectal, and Ovarian Screening Trial to develop an Early Detection Cancer Screening Trials Network to expand and accelerate laboratory and clinical research and the application of early detection technologies. $0.08 M
- Encourage collaborations among NCI-supported research centers, networks and consortia involved in translational research, including Cancer Centers, Specialized Programs of Research Excellence (SPOREs), Transdisciplinary Tobacco Research Centers, the Cancer Genetics Network, Clinical Cooperative Groups, Special Population Networks, the Early Detection Research Network, and the Mouse Models of Human Cancers Consortium. $0.50 M
- Expand the SPORE program by adding one SPORE each for gastrointestinal, brain, head and neck, and leukemia and lymphoma cancers; and two SPOREs each for ovarian and skin cancer. $24.00 M
- Establish a protected Web-based system for SPOREs, to exchange work in progress and research results to enhance inter-SPORE research. $0.50 M
- Expand the supplement programs for SPOREs, to stimulate inter-SPORE research projects and to conduct early clinical trials. $5.00 M
- Support expansion of infrastructure and methods for evaluating large scientific initiatives for translational research. $0.50 M

4. Expand the capacity of NCI Cancer Centers, networks, and consortia to disseminate proven interventions into communities and populations. **$15.00 M**

- Provide additional funding and seek funded partnerships with government and non-government organizations to perform research into cost-effective and efficacious dissemination of validated interventions for prevention, early detection, and treatment to practitioners, communities, and populations. $7.00 M
- Design ongoing Cancer Center infrastructure and mechanisms for practitioner, community, and population outreach to enhance the Cancer Centers' leadership role in disseminating proven interventions for cancer prevention and care for all. $8.00 M

Management and Support **$ 1.20 M**

Total **$79.53 M**

GOAL

Ensure that clinical trials address the most important questions in treatment and prevention, are broadly accessible, and enable strong translational research.

National Clinical Trials Program in Treatment and Prevention

The Challenge

As we decipher the molecular changes that cause a cell to become cancerous, a new paradigm in cancer treatment and prevention is emerging. Increasingly, new anti-cancer agents are directed at distinct molecular targets present within cancer cells, leaving healthy cells unharmed.[1] In light of the unique challenges arising from this paradigm shift, NCI must provide a versatile clinical trials system that will quickly and safely move proven anti-cancer interventions into healthcare settings where patients will benefit.

NCI provides leadership, resources, and expertise at all stages of clinical development for molecularly targeted agents. In the early stages of research, when candidate drugs are identified and shown to have promising potential, NCI forms collaborations and partnerships that help researchers from public, industrial, and academic settings to develop cancer fighting agents for a broader array of tumor types and at a faster pace than would otherwise be possible. After establishing proof-of-principle[2] in early clinical trials, researchers move on to verify the presence of relevant molecular targets in populations of patients and test for improvements in outcomes, such as tumor response, time to tumor progression, and improved survival. During this stage, NCI provides resources to test promising leads in large numbers of patients.

NCI has made substantial progress in building a clinical trials system that meets these requirements. However, a number of critical issues remain to be addressed. We must:

- Identify the most important questions in prevention and treatment that can be addressed through clinical trials.
- Create flexible mechanisms that allow for easy cooperation among basic scientists, clinicians, industry, academia, and NCI.
- Explore how molecular targeted therapies can be used in combination with conventional treatments or other molecular targeted agents.
- Develop surrogate endpoints[3] to improve the efficiency of small translational trials.
- Identify the most promising treatment or prevention agents for movement into large, easily accessible trials.
- Improve support to physician researchers.
- Improve access to clinical trials by physicians and their patients.
- Help ensure that treatments are made available to all patients who need them.

Progress Toward Meeting the Challenge

Building the Capacity for Successful Clinical Trials Research

As more private sector companies are beginning to develop anti-cancer drugs, NCI is expanding its role in public-private partnerships. Because pharmaceutical companies tend to seek FDA approval or licensing of a new agent for a single or few tumor types, NCI can help ensure that new agents are evaluated against a fuller range of cancers (or pre-cancers) and in combination with treatments such as surgery, radiation therapy, or other drugs. In one recent success, the **collaboration between Novartis Pharmaceuticals and NCI-supported researchers** led to the development of imatinib (previously called Gleevec™) to treat chronic myelogenous leukemia and now gastrointestinal stromal tumors.[4] In another public-private partnership, the arthritis drug celecoxib is being tested as a targeted drug for colorectal cancer prevention and treatment.

[1] See Molecular Targets of Prevention and Treatment, pages 60-64.
[2] In proof-of-principle studies investigators demonstrate that an agent has the desired biological effect on its target.
[3] Surrogate endpoints are based on laboratory measurement of some biological indicator of a drug's effectiveness rather than on longer-term outcome measures.
[4] See sidebar, this chapter.

Treatment with Imatinib Builds on Early Success

In May 2001, the U.S. Food and Drug Administration (FDA) gave fast track approval to the molecularly targeted drug imatinib (then called Gleevec™ or STI571) for the treatment of chronic myelogenous leukemia. Imatinib blocks the cancer causing effects of a genetically altered protein commonly found in this disease.[5] More recently, the FDA approved imatinib for treatment of gastrointestinal stromal tumors (GIST), a cancer caused by genetic modification of another imatinib-sensitive protein. GIST is a relatively uncommon but high-mortality cancer, notoriously resistant to any kind of chemo- or radiation therapy. When given to GIST patients in clinical trials, imatinib either dramatically reduced tumor size or arrested tumor growth. Clinical trials are underway to test the use of imatinib in treating over 15 other cancers. Some patients have already responded remarkably, including a chronic myelomonocytic leukemia patient whose blood was completely cleared of cancer in only one month.

Despite these unprecedented successes, researchers are finding that, for a number of reasons, many patients with advanced stage disease eventually stop responding to imatinib therapy. Based on intensive research, investigators are identifying strategies to overcome imatinib resistance, including treating patients with a combination of molecular targeted drugs early in the course of their illness.

[5] For more detail on this Story of Discovery, go to **plan2003.cancer.gov**.

NCI also recognizes the increasing need for **collaboration with laboratory scientists in conducting clinical trials for molecular targeted agents.** The cellular pathways and interactions involved in these molecular targets are extraordinarily complex and inter-related, and they require scientists to develop new techniques and tests to identify patients whose tumors contain the relevant targets and to monitor drug effects during treatment. More than half of NCI-sponsored cancer treatment trials initiated over the last two years have included correlative studies with laboratory scientists and this trend is increasingly seen in cancer prevention trials.

NCI continues to simplify the **administration of clinical trials** to make it easier for physicians and their patients to participate in NCI-supported trials. In 2000, we launched the online Cancer Trials Support Unit (CTSU) site to centralize the common administrative, financial, and data collection activities of its clinical trials cooperative groups. Since May 2002, CTSU physicians outside NCI cooperative groups have also been able to enroll patients into these NCI-sponsored clinical trials. NCI's efforts are having a noticeable effect, with accrual to NCI-sponsored cancer treatment trials increased by an unprecedented 18 percent in 2001.

Making Strides in Cancer Treatment through Clinical Trials

NCI's focused investment in clinical trials is paying off with increased survival and better quality of life for patients with a variety of cancers. Just a few of the advances emerging from recent clinical trials are listed here:

- Adjuvant therapy with oxaliplatin provides a modest survival advantage to some colorectal cancer patients who undergo conventional chemotherapy.[6]
- Tamoxifen, a targeted agent that has been shown to improve survival in some women with breast cancer when given together with chemotherapy, improves disease-free survival even better if given when chemotherapy has been completed.
- Treatment with high doses of the drug methotrexate improves the event-free survival of children with T-cell acute lymphoblastic leukemia (ALL) as well as or better than any other drug reported in the medical literature. The trial is an example of the type of research that has led to a 75 percent decline in mortality rate for children with ALL over the last 27 years, through improvement of conventional cancer therapies.

Making Strides in Cancer Prevention through Clinical Trials

From years of scientific research, we know that cancers are not caused by a single, catastrophic event, but result from a complex and long-evolving process. Since many cancers take decades to develop, we have the time and opportunity to intervene to stop or reverse its progress before patients become sick. NCI's clinical trials for cancer

[6] See page 11 for more information.

National Clinical Trials Program in Treatment and Prevention

G O A L

Ensure that NCI's clinical trials program is poised to address the most important medical and scientific questions in cancer prevention and treatment quickly and effectively through state-of-the-art clinical trials. Ensure that the trials are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for them. Incorporate relevant correlative laboratory studies into clinical trials to enable strong translational research.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Identify and develop the most promising new agents for cancer treatment and prevention. **$84.50 M**

- Expand partnerships and create flexible collaborations with industry, the FDA, and other public, private, and academic organizations to speed development of promising agents and to bring together the best laboratories, institutions, and investigators (including surgeons, pathologists, and radiologists, in addition to traditional participants) for early translational research. $4.00 M
- Expand resources for the Rapid Access to Intervention Development and Rapid Access to Prevention Intervention Development programs. (See page 62, Objective 4.)
- Expand capacity to file Investigational New Drug Applications and New Investigational Technology Applications to facilitate early proof-of-principle clinical trials. $0.50 M
- Create broadly based working groups to identify clinically relevant surrogate endpoints. Develop resources and standardize assays, approaches, and clinical trial designs to validate these endpoints. $2.00 M
- Build translational research capacity to use correlative studies more extensively. $8.00 M
- Increase funding for Interdisciplinary Research Teams for Molecular Target Assessment to develop resources to assess the effects of promising agents on their molecular targets. $20.00 M
- Develop molecular assays required to characterize/classify tumors, and make them widely available. (See page 62, Objective 2.) Support a national tissue resource system to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified.
- Increase the pace of development and clinical testing of promising new therapeutic and preventive agents by (1) substantially increasing the number of promising agents entering NCI-sponsored clinical trials over the next two to three years as well as the number of pivotal early clinical trials, (2) tripling annual patient accrual to early clinical trials of promising agents, (3) providing financial incentives for timely initiation of clinical trials and adherence to developmental milestones, and (4) expanding the rapid grant review process, Quick Trials, for mechanism-based clinical trials. $35.00 M
- Support the NCI intramural clinical trials program by increasing the number of data managers, research nurses, biostatisticians, and clinicians available to support a critical mass of clinical investigators, and continuing the Tissue Array Research Program to identify key molecular alterations in cancers. $15.00 M

2. Strengthen scientific planning and leadership for the large, definitive clinical trials that evaluate and define the efficacy and clinical benefit of new treatments and prevention strategies. **$26.00 M**

- Identify and address compelling clinical questions confronting physicians and their patients under treatment for cancer or at high-risk of cancer. $17.00 M

- Expand State-of-the-Science meetings to identify important research questions and define a scientific research agenda to address them. $1.00 M
- Expand clinical trials planning to address critical questions across the major types of conditions experienced by patients by (1) integrating cross-disciplinary input (e.g., oncology and diagnostic imaging) and project teams into scientific strategic planning and (2) incorporating evaluation of relevant biomarkers as well as behavioral, epidemiologic, outcomes, and other research into existing treatment and prevention trials to address questions in specific tumor types and patient populations. $1.00 M
- Provide additional research funds for leadership support of scientists who are responsible for writing, monitoring, and analyzing NCI-sponsored, high-priority Phase III trials: researchers who chair studies in addition to caring for patients, and study statisticians. $3.00 M
- Increase funding for tissue banks (collection and storage of patient tissues from large clinical trials with accompanying patient data). This will enable correlative studies and long-term follow-up for future evaluation of new assays and markers. $4.00 M

3. Double the rate at which Phase III trials are completed. **$223.50 M**

- Increase the number of patients accrued to national trials, and shorten the duration of accrual, to substantially increase the number of new treatments or interventions that can be evaluated. Increase funding for nursing, data management, and other infrastructure costs at local clinical trial sites, and for operations, data management, and statistical offices. Increase the number of (and the capacity of existing) Community Clinical Oncology Programs.
- Facilitate participation of new clinical trials investigators through a "start-up" loan program (repayable by reduced future reimbursements) for training, research nurse support, and data management.
- Provide extensive information about treatment and prevention clinical trials to enable patients and physicians to make informed choices. With the NCI Office of Communications, patient advocacy groups, and others, create educational, marketing, and communications strategies to inform patients and physicians about clinical trials. Develop novel strategies, including the use of alternative media, for working with minority and under-represented patient populations and their primary care physicians.
- Expand the Cancer Trials Support Unit to consolidate administrative tasks and to provide a single interface for investigators to enroll patients. Develop uniform electronic case report forms and data reporting systems. Expand NCI's audit program to ensure continued high quality accurate data from new sites and increased accrual to clinical trials.
- Provide funding directly to participating patients with special needs to cover costs associated with travel, childcare, and other relevant limiting expenses. Work with state and local government agencies to address barriers to access for patients dependent on state health agencies for healthcare coverage.

4. Reduce outcome disparities caused by lack of access to trials or follow-up care.

- Increase access of underserved populations to state-of-the-art clinical trials. (See page 87, Objective 4).
- Encourage local sites to identify existing resources for helping underserved patients receive appropriate follow-up care and ensure that follow-up care is offered.

Management and Support **$ 6.10 M**

Total **$340.10 M**

The Next Step in Targeted Therapy — Hitting Multiple Targets

Scientists know that cancer develops as a result of mutations in genes that in turn alter the normal structure of certain proteins (those that regulate cell growth and other critical functions). These genetically altered proteins disrupt "cellular pathways," or the ordered interactions among the diverse molecules in the cell, resulting in uncontrolled cell growth and cancer. As scientists gain a better understanding of these molecular changes, they are able to develop drugs designed to stop cancer development in its tracks by targeting the faulty proteins that wreck havoc on normal cellular pathways.

Increasingly, however, investigators are learning that targeting one protein or one pathway is not always enough. Cellular pathways are tremendously complex, involving intricate and ordered contact among thousands of molecules. As one targeted pathway is shut down within its cells, the tumor may begin to die, but then start growing again. It may be that an alternate pathway, one not affected by the drug, is able to perform the same function as, and thus compensates for, the targeted pathway. This type of "cellular redundancy" occurs naturally and, although it is healthy and beneficial in normal cells, it makes cancer cells harder to kill. To contend with this reality, researchers have begun developing drug treatments that use combinations of targeted drugs to simultaneously shut down alternate pathways so that the cell cannot escape the effects of treatment. Furthermore, since some patients are resistant to one type of drug but not another, using combinations of drugs targeting critical junctures of multiple pathways should increase the patient's chances for successful treatment.

prevention seek to determine which person is at risk for cancer; define ways to prevent or reduce that risk; detect cancer at its earliest stages; and actively intervene to prevent invasive cancer. The following represent a small sampling of the progress in these areas:

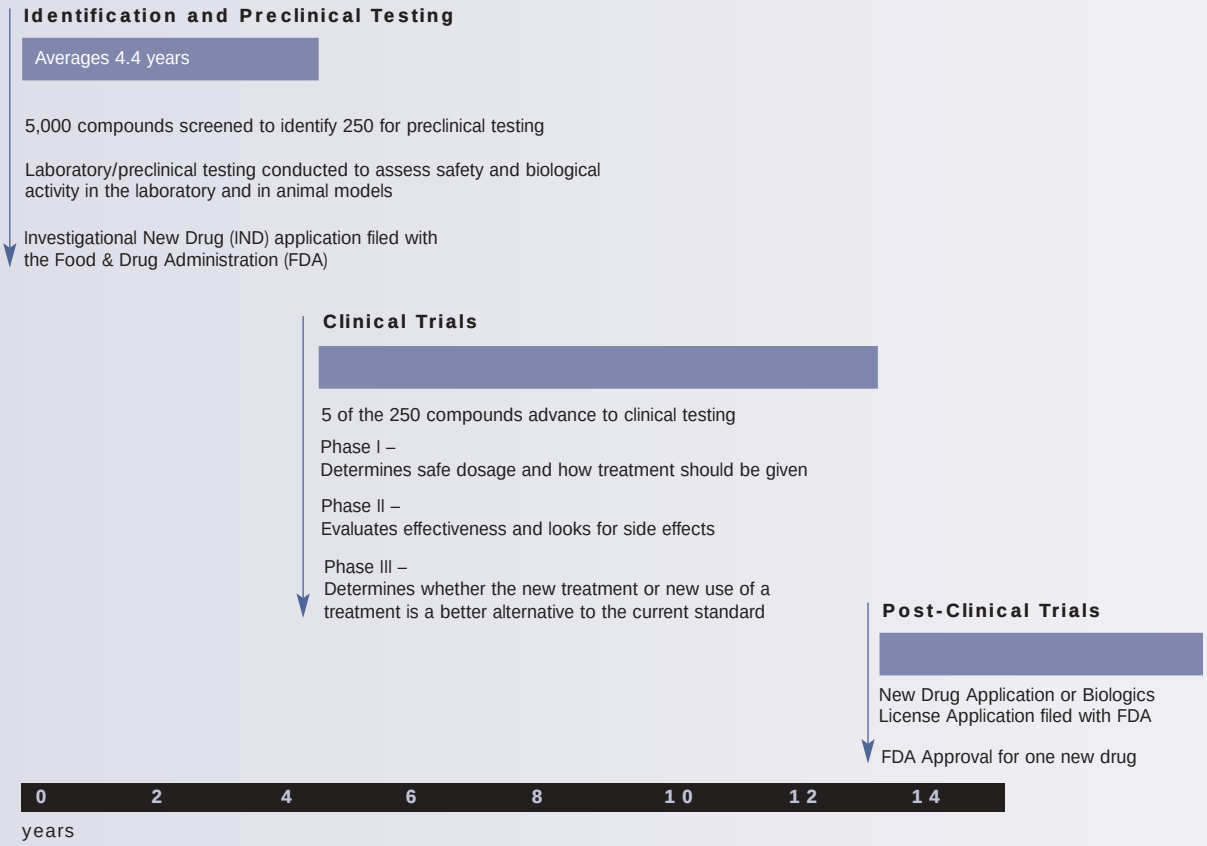
- Because some women suffer serious side effects from tamoxifen, NCI is sponsoring clinical trials for other preventive agents, such as raloxifene, an osteoporosis prevention drug. NCI-supported researchers are also developing risk assessment tools to determine which patients are most likely to benefit from various prevention strategies with the fewest side effects.
- The newest prostate cancer prevention trial, the Selenium and Vitamin E Cancer Prevention Trial, was launched in July 2001. The 12-year study will answer whether or not seven or more years of daily dietary supplementation with selenium and/or vitamin E will reduce the incidence of prostate cancer. Of note, one third of the 32,400 men needed were accrued within the first eight months of the trial. Serum and white blood cells are being collected for correlative laboratory research and preliminary results from early studies are encouraging. Studies examining cells grown in the laboratory have suggested that selenium might slow the growth of prostate cancer and kill the cancerous cells by apoptosis — a cell suicide mechanism.
- Investigators recently discovered that patients with a history of colon polyps might reduce their risk of developing colon cancer by taking low doses of aspirin in addition to having their regular colorectal cancer screenings.

Drug Discovery and Development — A Life Saving Investment

Discovering and developing new treatments for cancer is a lengthy and expensive process. But therapeutics that use the latest knowledge and the best technology are absolutely essential for us to move forward in our fight against cancer. The process begins in laboratories at university, research institute, government, or industrial facilities where individual or groups of scientists identify possible drug agents to target cancer. Once identified as potential agents, compounds must be screened, tested, and used successfully without serious adverse effects in clinical trials.

Preclinical testing validates the safety and biological activity of a compound in the laboratory and in animal models. Clinical trials determine safe and most effective dosages, how a treatment should be administered, its efficacy, and patient outcomes. At any point in this drug development process, researchers may discover that the compound does not work in quite the way they were hoping. Animals have such intricate molecular biology that a drug that effectively disrupts cancer development in isolated cells may behave differently in a mouse, and differently still in a human. When a drug does not work, researchers must decide whether to abandon that compound or take it back to the laboratory and try to modify it. Once these steps are completed, new drugs must then be approved by the Food and Drug Administration through a rigorous process before they can be used to treat cancer.

Only one in 5,000 compounds or fewer make it to FDA approval. The total length of time from initial discovery to FDA approval averages around 15 years and the total cost can be as high as $500 million to develop a single new drug. As we attempt to design or discover more targeted therapeutics, the costs may be even higher. However, only through this painstakingly thorough process of drug discovery and development do the many lifesaving cancer drugs coming out every year reach the patients whose lives are touched by them.



GOAL

Create a cancer informatics infrastructure to support and integrate the full spectrum of cancer investigations.

Developing Bioinformatics for Cancer Research

The Challenge

Bioinformatics is the art and science of electronically representing and integrating biomedical information in a way that makes it accessible and usable. Each discipline involved in the immense complex of cancer research generates volumes of data and research findings, all contributing vital threads of insight that bioinformatics specialists must weave together into a tapestry of knowledge. The challenge is to use electronic standards to devise systems that allow different sets of data to "talk" to one another. Such systems make it possible for scientists to use this new "in-silico" biology to generate hypotheses; conduct virtual experiments using large collections of data from multiple sources; and create, manage, and communicate massive amounts of new knowledge in practical timeframes.

The challenge of integrating separate scientific vocabularies and insight is daunting because of the vastness and rapid evolution of the data. New models and tools are needed to allow scientists to bridge language, integrate concepts and information, and enable complex analysis. In this way, information systems will be a vital, dynamic tool in the hands of cancer researchers. To address these challenges, NCI is pioneering a versatile informatics infrastructure, requiring us to:

- Help incubate the next generation of bioinformatics applications and insights to support cancer research.
- Establish partnerships with commercial, academic, and other governmental groups engaged in bioinformatics research and development, thus broadening our base of components, compatible tools, and data.
- Expand training and support for scientists pioneering the application of bioinformatics in cancer research.

Progress Toward Meeting the Challenge

Constructing a Cancer Knowledge Resource

One of our key tasks has been to develop the ability to classify, locate, and distribute units of cancer-related information, such as the description of a gene or a process, the email address of a principal investigator, or a reference to a published paper. Data are transformed into information components, which can then be combined to generate knowledge. Our system is called the **cancer Common Ontologic Reference Environment** (caCORE). The caCORE is composed of three interacting layers. At its foundation is NCI's **Enterprise Vocabulary Services**, which organize and translate the distinct but overlapping vocabularies of disparate scientific projects via a common vocabulary.

The middle tier of caCORE contains ways of collecting scientific data or **Common Data Elements** that conform to the international standards used by other Federal organizations. This keystone effort will ensure that all data from NCI-supported programs, whether from clinical trials, animal model programs, basic research, or other disciplines can be easily shared.

The top layer of caCORE is composed of models of information — the **cancer Bioinformatics Infrastructure Objects** (caBIO). The objects capture the expertise within the disciplines that constitute cancer research, allowing the knowledge to be shared through computer tools. The current collection of objects captures knowledge in the areas of genomics, genetics, animal models, and clinical trials. caBIO is built with open source software, making it available to scientists without restriction.

Collecting and Sharing Cancer Research Data

The data and findings produced through NCI initiatives are valuable not only to the investigators who generate them but also to other cancer researchers. They form a foundation on which to build future studies and a resource for "in silico" biomedical experiments. Some examples follow.

- We have constructed a repository for the mouse models developed by the cancer research community through the Mouse Models of Human Cancers Consortium. The repository is called the **Cancer Models Database**.[1] It contains models that can be used to further explore cancer's origins and to test new therapies. The database allows researchers to share the insights they have gained in their investigations. It also permits additional investigators to extend the work of the model generators, building directly on the base they have constructed and accelerating the rate of discovery.
- We have created a repository called the **Gene Expression Database Portal**[2] to provide an integrated system for researcher access to tumor genetic and molecular taxonomy data enabled by initiatives such as the NCI's Directors Challenge: Toward a Molecular Classification of Cancer and the Mouse Models of Human Cancers Consortium.
- We continue to expand the collection of publicly accessible genomic data generated by the Cancer Genome Anatomy Project and to expand the use of state-of-the-art informatics tools through collaboration with the Cancer Therapy Evaluation Program.

Building a Network of Interoperable Analytic Tools and Data Sources

NCI has begun the process of establishing a network of bioinformatics tools and data that interact to capture the innovation of the cancer research community and facilitate the use and re-use of its valuable resources, such as tissue repositories.

- A first step in building the network has been the **construction of Internet portals** through which various network and consortia communities can share their tools and data.
- NCI is working with the American Association of Cancer Institutes to build a **clinical trials network** that distributes information, available to all, on those trials that are conducted at participating Cancer Centers.
- NCI is leading a consortium of industry, academia, and government agencies to develop an interoperable infrastructure for biomedicine, the **Interoperable Informatics Infrastructure Consortium**.

Fostering Application of In Silico Biomedicine in Cancer Research and Care

Early applications of in silico biomedicine in cancer research supported by NCI confirm the promise of this exciting new scientific approach. These efforts

[1] cancermodels.nci.nih.gov/mmhcc
[2] gedp.nci.nih.gov

Bioinformatics: Linchpin of Translational Science

Translating results from the laboratory bench to bedside delivery of patient care and communicating the lessons learned back to the bench, goes far beyond the high-speed calculation, the once-unimaginably complex modeling, and the massive storage and retrieval used for individual studies in individual institutions. It demands a whole system of linkages across laboratories, clinics, disciplines, and organizations, from purely research to regulatory, to journalistic, to advocacy, and beyond. At the National Cancer Institute, we recognize that bench-to-bedside translation is conceptually inseparable from informatics. Our success with one will continue to reciprocally drive our success with the other.

Developing the bioinformatics infrastructure requires that we build greater power and compatibility at several levels of focus, and at several points in the process, building pioneering systems that, in working together, make it easier for the scientists who use them to work together as well. The codes and logic that form the language for integrating these systems can then be standardized. In many cases, the standards themselves must be created, tested, and agreed upon.

Research highlights in this section illustrate application of these prototype informatics systems, ranging from the micro level for discovering meaningful patterns in bits of genetic material to the macro for monitoring clinical trial activity, to the most broadly focused for tracking and comparing activity, so that we can know how well our funding is meeting the full range of research requirements.

Developing Bioinformatics for Cancer Research

GOAL

Create a cancer informatics infrastructure that enhances information and resource exchange and integration among researchers and clinicians working in diverse disciplines, to facilitate the full spectrum of cancer investigations.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Expand NCI's core informatics infrastructure to support and integrate NCI-supported basic, clinical, translational, and population research initiatives. **$ 49.00 M**

- Provide additional support and enhance integration of data and development of tools emanating from NCI's Extraordinary Opportunities. Facilitate information exchange within NCI-supported research initiatives. Support Specialized Programs of Research Excellence and Cancer Center efforts. $29.00 M
- Establish a toolbox of open-source informatics applications and services based on a common set of operating principles that support NCI's diverse cancer research activities. $5.00 M
- Expand the research infrastructure that uses the NCI "knowledge stack," assembling common vocabulary, standard data elements, and information models to further the exchange of all types of cancer information and data among the cancer community. $5.00 M
- Expand information technology-based support services to enhance planning, execution, and communication of the wide-ranging research portfolio supported by NCI. $10.00 M

demonstrate that bioinformatics can be used to refine diagnosis and improve screening.

Facilitating Discovery through Integration Tools. NCI has undertaken the **Cancer Molecular Analysis Project** to facilitate the identification and evaluation of molecular targets in cancer by integrating comprehensive molecular characterizations of cancer. Both the data and infrastructure are publicly accessible.[3]

Improving Cancer Diagnosis and Screening through Bioinformatics. Recent successes demonstrate the immense potential for the use of bioinformatics tools, specifically **artificial intelligence**, to improve cancer diagnosis and screening.

- Effectively and safely treating pediatric acute lymphoblastic leukemia (ALL) requires detection of subtle distinctions among several subtypes. Pinpointing the subtype usually requires the combined efforts of a hematologist/oncologist, a pathologist, and a cytogeneticist. NCI-supported researchers have used artificial intelligence to analyze samples from patients whose diagnoses had already been determined. Their new test is 95 percent accurate. Moreover, they identified a new subtype of ALL.

[3] **cmap.nci.nih.gov.** The Cancer Molecular Analysis Project application permits investigators to discover molecular targets, assess their validity and interaction with other targets, determine if there are therapeutic agents that can act on this target, screen for possible toxicity, and determine whether there are clinical trials evaluating these agents.

2. Create a community matrix of interoperable data sources, analytic tools, and computational resources that provide informatics capability for the cancer research community. **$21.50 M**

- Enable other organizations' information systems to work seamlessly with ours. Establish a minimum of 5 academic, government, and commercial strategic partnerships in a research park setting where all partners can work together to address bioinformatics questions. $15.00 M
- Use a minimum of 20 investigator-based awards that build on the NCI informatics core to (1) deploy resources to the cancer research community to serve as the foundation for additional infrastructure and (2) facilitate rapid deployment of related new research initiatives. $6.50 M

3. Expand the capacity of cancer research institutions to perform interdisciplinary informatics research. **$11.50 M**

- Establish a network of bioinformatics research centers to work with and through the NIH Biomedical Informatics Science and Technology Initiative. $5.00 M
- Supplement funding to NCI-supported research organizations to support investigator-initiated research to access state-of-the-art biocomputing tools and data. $6.50 M

4. Support bioinformatics training for both experienced and new scientists. **$ 3.00 M**

- Recruit new scientists through 20 development awards. $1.50 M
- Cross train experienced scientists through transition awards. $1.50 M

Management and Support **$ 3.00 M**

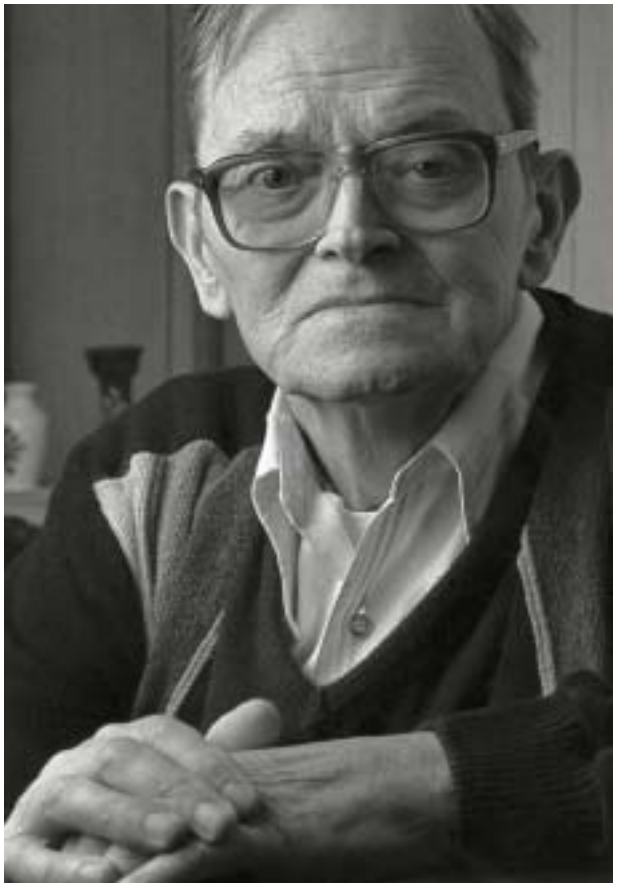
Total **$88.00 M**

- NCI scientists have analyzed microarrays using an artificial intelligence technology called neural networks to distinguish among members of a family of childhood tumors that include neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, and Ewing tumors. The results of this kind of analysis hold promise for enabling healthcare providers to select appropriate treatment options and determine possible outcomes for patients.

- NCI scientists have found that patterns of proteins in patients' blood serum may reflect the presence of disease and have used serum proteins to detect ovarian cancer, even at early stages. The research, a collaboration of the Food and Drug Administration, the NCI, and a private company, unites two exciting disciplines: proteomics, the study of the proteins inside cells, and artificial intelligence computer programs. Scientists were able to "train" the computer to distinguish between patterns of small proteins found in the blood of cancer patients and those of people not known to have the cancer. The artificial intelligence program identified exquisitely subtle differences in the patterns that may distinguish between women with ovarian cancer and women with noncancerous conditions.

The Interface of Aging and Cancer

The risk of developing cancer increases with age. Because of this vulnerability for our Nation's aging population, NCI is conducting innovative research to better understand the relationships between aging and the development and progression of cancer. Further work is needed to fully address the interface of aging processes with cancer detection, diagnosis, and pre-treatment evaluation as well as the efficacy and tolerance of anti-cancer drugs in older patients.



By 2030, 20 percent of the U. S. population will be over 65 and the number age 85 years and older will have more than doubled in size from 4 million to approximately 8.5 million. Close to 58 percent of all newly diagnosed malignancies and 71 percent of all cancer deaths are in persons 65 and older according to the NCI Surveillance, Epidemiology, and End Results (SEER) program data for 1995-1999. As people live longer, more will experience cancer. As a result, there will be more cancer survivors, many of whom will experience residual problems that impact their quality of life.

Growing older as a cancer survivor also increases one's chances of developing other health problems, disabling conditions, and the recurrence of cancer.

Cancer statistics, demographic projections, and epidemiologic perspectives combine to illustrate the need to develop cancer control and cancer research strategies that address the magnitude of the cancer problem for current and future older Americans. NCI and the National Institute on Aging (NIA) have partnered to integrate crosscutting aging and cancer research and focus funding within existing research priorities. The research includes the biology of aging and cancer, the impact of aging on cancer treatment, the quality of survivorship, symptom control, and disease-specific studies.

Biology of Aging and Cancer

Older patients differ from younger cancer patients in susceptibility to disease progression and response to treatment. The underlying mechanisms of cancer and aging overlap in the study of tumor initiation, progression, and maintenance. Studies to better identify the molecular alterations in carcinogenesis related to the aging process intersect a number of NCI priority areas.

- **Genes and the Environment** studies examine genetic changes, environmental influences, and host factors such as oxidant stress and cell death that may alter tumor progression in the aging patient.
- **Signatures of Cancer** studies focus on the interaction of normal aging cells and cancer cells within the tumor microenvironment, differences in the manifestation of cancer types in older and younger patients, cellular and molecular characteristics that distinguish between

those patients who could benefit from aggressive therapy and those who could be spared further therapy, and molecular alterations in carcinogenesis that are related to aging cells.

- **Cancer Imaging** studies have led to an expanding array of diagnostic procedures such as the use of magnetic resonance probes, radiopharmaceuticals, and optical probes to reduce cancer treatment side effects and optimize recovery for older patients.
- **Quality of Cancer Care** studies link the NCI SEER cancer registry to Medicare and other insurance data to assess the quality of cancer care and survivorship for older patients, early and late effects of treatment, occurrence of multiple primary tumors, and methodology for assessment and reporting.

Improving Cancer Outcomes, Survivorship, and Symptom Control for the Aging

We know that current healthcare practices frequently fall short of providing the best available early detection, treatment protocols, and quality care that older patients deserve. Studies show that older people are less likely to be screened for prevalent cancers such as breast, colorectal, and cervical disease. Older patients receive care for symptom control less frequently because of inadequate standards of care. For example, a 1998 study of cancer patients in nursing homes found that 26 percent of patients with daily pain received no analgesics. A number of NCI-supported studies focus on issues of cancer treatment and care for older people.

- The **National Clinical Trials Program** works to increase the accrual of people 65 and older to early trials through NCI Cooperative Groups and develops trials that are specifically designed for older cancer patients. Trials for new agents and toxicology models include efficacy and tolerance evaluations in the aging. Another important area for evaluation is radiation therapy in the older patient, including trials for tolerance to conventional and combined modality therapy as well as assessment of novel radiation with the potential for treatments that are faster and less morbid.
- **Quality of Cancer Care** studies focus on developing guidelines for treatment decisions that assess co-morbid conditions and the limited functional reserve of the older person. Researchers are investigating the effects of multiple health problems on early detection, diagnosis, prognosis, and treatment of older cancer patients. Other studies test the efficacy of current methods of symptom management in older patients using evidence-based guidelines.
- **Survivorship** studies identify potential short- and long-term medical effects induced by treatment such as susceptibility of the older patient to multiple primary tumors, anti-tumor drug alterations, and cancer recurrence. Future research will focus on developing methods to prevent or offset these problems in older persons.
- **Molecular Targets of Prevention and Treatment** studies examine the human biology of cancer and aging that reveal which aspects of tumor biology and tumor growth vary by age. These investigations have the potential to provide information that could lead to tailored therapeutic approaches.

Several recommendations for engaging NCI-supported Cancer Centers in pioneering research on issues faced by older cancer patients and their care givers came out of a June 2001 workshop jointly sponsored by NCI and NIA. For a full report on the workshop, go to **nia.nih.gov/health/nianci**.

Studying the Impact of Colorectal Cancer on the Older Patient

Colorectal cancer is third in cancer incidence and mortality in the United States. SEER data for 1995-99 show that 70 percent of the incidence of colon and rectum tumors are in individuals 65 years and older. Yet, there is a paucity of attention to older persons affected by these cancers. A much-needed knowledge base would include:

- Surveillance of persons at high risk
- Influence of concomitant age-related problems
- Gender and racial differences
- Pathogenesis of colorectal cancer
- Influence of coexisting diseases
- Criteria for older surgical candidates
- Modification of surgery procedures in older patients
- Preoperative assessment to assist surgeons in prognosis and treatment

When cancer survivors and their loved ones ask me what NCI is doing to cure or prevent cancer, I tell them that we are finding many of the pieces of the cancer puzzle, and are learning what additional pieces to look for and where they probably fit. Cancer research has entered a whole new phase in how we identify and assemble the pieces. — *Andrew C. von Eschenbach, M.D.*

Advancing Discovery and Its Application

Part of the story is about how we are probing and discovering events at the molecular level and in the behavior of particular proteins. But molecules don't smoke and proteins don't neglect to wear sun protection, and genes don't make the decision to join clinical trials of new treatments.

So the story also includes research into lifestyle and behavioral factors and environmental exposures that so profoundly affect the burden of cancer. Once we more fully understand cancer-related molecular, cellular, microenvironment, behavioral, psychological, and social influences, we can develop more effective and less harmful approaches to cancer prevention, detection and diagnosis, treatment, and control.

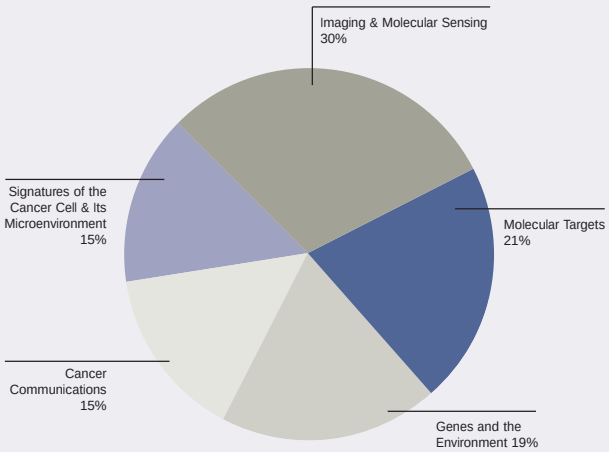
For Fiscal Year 2004, NCI's scientific priority areas to accelerate the pace of research and its application include Extraordinary Opportunities for Investment in *Genes and the Environment*, *Signatures of the Cancer Cell and Its Microenvironment*, *Molecular Targets of Prevention and Treatment*, *Cancer Imaging and Molecular Sensing*, and *Cancer Communications*. Increased investment in these areas is at the core of our ability to:

- Understand the causes, risks, detection, diagnosis, and treatment of cancer and how to communicate this information effectively to all populations.
- Develop interventions based on these scientific insights.
- Ensure dissemination of interventions to all who need care.

FY 2004 Increase Request for Advancing Discovery

(dollars in thousands)

Genes and the Environment	$ 51,800
Signatures of the Cancer Cell & Its Microenvironment	$ 41,200
Molecular Targets	$ 54,800
Imaging & Molecular Sensing	$ 78,700
Cancer Communications	$ 39,750
Total	**$266,250**



G O A L

Discover genetic, environmental, and lifestyle factors and their interactions that define cancer risk and inform strategies for cancer control.

Genes and the Environment

The Opportunity

The debate over nature vs. nurture is as old as scientific inquiry itself. Is it a particular characteristic passed from one generation to another, or is it imposed by the world into which the individual is born? Especially with respect to cancer, that question has become far more difficult, because we now know that elements in the environment or a person's lifestyle can damage genes, and we are finding that some genes seem to require certain conditions to give rise to cancer, while others virtually guarantee its occurrence. We have been able to identify some of the human genes that make people susceptible to cancer, to apply increasingly sophisticated molecular technologies to analyze genetic changes, and to examine the relationship between disease development and individual genetic profiles. We have learned about a variety of carcinogenic environmental factors, including pollutants in air, water, and soil; components of food, tobacco, alcohol, and drugs; sunlight and other forms of radiation; and infectious agents.

Early efforts to discover how genes and environmental factors interact to cause cancer are showing promise but also highlight the complexity of the puzzle. Some genes have proven to be so powerful that their presence in an individual makes cancer highly predictable. For example, carriers of the gene for Familial Adenomatous Polyposis are almost certain to develop colon cancer. Mutations in the susceptibility genes *BRCA1* and *BRCA2* are risk factors for breast cancer that may arise from a combination of factors. Similarly, some environmental exposures, such as tobacco use, can be strong, but not certain, predictors of cancer.

We want to learn how certain environmental exposures increase the cancer risk for genetically susceptible subgroups and uncover elements of the gene-environment interaction that can lead to tangible improvements in our ability to prevent, detect, and control cancer. Once we can define the cancer risks associated with specific environmental and genetic factors and their interactions, we can then develop new individual and public health strategies to avoid adverse exposures, check genetic susceptibility earlier, and identify appropriate interventions and precautions for people at high risk.

To make progress in this area, NCI needs to develop new ways to study cancer susceptibility genes, environmental exposures, and their interactions and to maximize the availability and use of large amounts of population data, biospecimens, laboratory models, and other resources. Large-scale studies, like the cohort consortium described below, with new levels of interdisciplinary cooperation and innovation from the cancer community will be needed to achieve tangible improvements in clinical practice and public health.

Progress in Pursuit of Our Goal

The NCI is pursuing research opportunities in several growth areas to better understand cancer-related genes, environmental and lifestyle factors, and their interactions.[1]

Building Capacity through Large-Scale Collaborations

NCI is continuing to build the **Cohort Consortium** to address the need for large-scale collaborations in genetic epidemiology to unlock the full potential of new discoveries in genomics. This consortium is comprised of well established investigators who, individually, had initiated over 15 separate prospective studies of large population groups. Working together, the Consortium will pool high quality environmental exposure data along with information from biologic specimens suitable for genetic analysis from over 700,000 participants. One group within the

[1] See the progress report and plan for research on tobacco and tobacco-related cancers on pages 94-98.

Genes and the Environment

G O A L

Discover those genetic, environmental, and lifestyle factors and their interactions that define cancer risk and that can inform the development of new strategies for prevention, early detection, and treatment.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Identify new environmental risk factors and susceptibility genes and determine their interactions in cancer causation. **$13.00 M**

- Utilize the unique advantages of the Cohort Consortium to investigate exogenous and endogenous[4] exposures best studied in large populations and their interactions with susceptibility genes.
  - — Support developmental studies based on the Consortium's gene-environment study of breast and prostate cancers to determine the value of adding studies of other common cancer sites. $2.00 M
  - — Expand the number of participants, population diversity, and types of biospecimens involved in these studies. $2.00 M
- Support the Case-Control Consortium to fully investigate gene-environment interactions for specific types of cancer. Initiate large population-based and hospital-based studies to develop comprehensive data and specimen resources by cancer site. $5.00 M
- Continue improving the infrastructures needed for large, collaborative human population studies with biospecimen components.
  - — Maximize the efficiency and cost effectiveness of specimen collection, processing, storage techniques, and high-throughput assays for human population studies. $2.00 M
  - — Enhance the capacity of informatics systems developed to capture, store, analyze, and integrate the massive amount of information generated by these studies. $2.00 M
- Support studies to determine the contribution of inflammation, injury, and infectious agents to the genesis of lung cancer, a need identified by the Lung Cancer Progress Review Group.

2. Develop new ways to assess and measure environmental exposures for use in population studies. **$ 5.00 M**

- Continue expanding the Innovative Molecular Analysis Technologies Program to develop new non-invasive techniques for collecting and analyzing genes and gene products in very small biologic samples. $2.00 M
- Continue support for applying and validating measures of the cumulative cellular, genetic, and molecular effects of environmental exposure through funding supplements for ongoing research programs. $3.00 M

[4] An exogenous exposure originates from outside the body. An endogenous exposure originates from within the body.

3. Identify cancer predisposing genes in high-risk families and investigate how other genes and environmental factors modify expression of these genes. **$ 9.00 M**

- Fund new consortia to identify susceptibility genes that remain to be discovered as well as other genetic and environmental modifiers of risk. $5.00 M
- Support interdisciplinary studies for gene discovery and characterization in new collaborative family registry groups. $2.00 M
- Support collection of fresh frozen tumor tissue and other biospecimens from cancer prone families for microarray based molecular signature analyses. $2.00 M

4. Develop tools for the study of gene and environment interactions in human populations. **$ 3.00 M**

- Extend the Genetic Annotation Initiative to identify new gene variants and explore various molecular applications.
- Support the breast, colon, prostate, and pancreatic cancer comparative genetics work groups employing mouse models to help localize cancer susceptibility genes in humans and determine their function. $3.00 M

5. Support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility. **$19.00 M**

- Sustain the Cancer Genetics Network as a resource for studies of clinical care for early detection, diagnosis, and treatment of genetically high-risk individuals, including those from minority and underserved populations. $11.00 M
- Expand support for studies in cancer genetics that examine psychosocial responses to cancer risk communication to inform the development of effective educational strategies and resources for patients, providers, and the public. $4.00 M
- Support research on the role of genetic factors and their interactions with physiologic and/or psychosocial factors among survivors of cancer. $2.00 M
- Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer. Merge genetics based and environmental models. Refine models that predict risk and other outcomes among diverse populations. $1.00 M
- Collaborate with the Centers for Disease Control and Prevention Genomics and Public Health Centers to improve understanding of the value of family history in predicting the risk of cancer and translating this information into clinical practice and public health programs. $1.00 M

Management and Support **$ 2.80 M**

Total **$51.80 M**

Consortium has developed a truly novel four-year collaborative study to identify critical gene-environment interactions in endogenous hormone pathways for over 7,000 cases each of breast and prostate cancer. A second group is pooling data for less common cancers, such as pancreatic cancers.

The **Case-Control Consortium** is also investigating genetic and environmental determinants of cancer. For non-Hodgkin's lymphoma, several investigators who have completed individual studies and collected biologic specimens, are formulating a combined study to give them the statistical power to uncover key gene-environment interactions. A second group of investigators, members of the NCI-supported HMO **Cancer Research Network**, is pooling its resources to develop the largest case-control study to date of pancreatic cancer. These researchers will employ "real time" electronic reporting of pathology, laboratory, radiology, and outpatient physician visit findings, resulting in the rapid identification of pancreatic cancer within ten working days. The purpose of this study is to develop a better understanding of risk factors for sporadic and familial pancreatic cancer and ultimately to use this knowledge for earlier detection and prevention.

Assessing and Measuring Environmental Exposures

Few population studies have investigated the question of whether environmental endocrine disruptors[2] have a role in adverse health effects, including cancer in humans. NCI is collaborating with the National Institute for Occupational Safety and Health, the Environmental Protection Agency, and the National Institute of Environmental Health Sciences to **study organochlorine pesticides and polychlorinated biphenyls** (PCBs) and their possible association with testicular and breast cancer risk. Researchers are following groups of infants born to mothers exposed to very high versus low (background) levels of PCBs through childhood and adolescence. The study provides a unique mechanism to assess whether early life exposures are critical in the eventual occurrence of cancer.

NCI is funding 12 grants for **geographic based research in cancer control and epidemiology.** Half of these projects will apply innovative methods for assessing difficult to measure environmental exposures. One such innovation will use satellite imagery to estimate potential exposure to agricultural pesticides. The other grants will be used to develop methods and software to detect geographic patterns and clusters of cancer rates and to explore associations with environmental, sociodemographic, and access to care factors.

The recently completed **Observing Protein and Energy Nutrition Study** assessed the measurement error inherent to studies in which patients must complete questionnaires or surveys to report their dietary intake. Investigators conducting this study, the largest ever of its kind, are comparing self-reported dietary intake data from 484 men and women with biomarkers that will reflect the actual diet of the patient. The results of the study will give us a better grasp of the reporting error so that we can more accurately interpret the findings of self-report dietary studies.

Molecular profiling using innovative micro-technologies may be used to examine chromosome alterations and changes in protein levels following exposures to various environmental toxins that correlate with the appearance of cancer. For example:

- Scientists have found that changes in the levels of particular proteins (those whose genes may be altered by the biochemical process of methylation) have been associated with the development of cancer. NCI-funded molecular micro-technology research may permit identification of new environmental exposures that change the number of these important proteins in tissues.
- Chromosome alterations in cancers are common and complex and often difficult to assess. New molecular technologies may be used to rapidly identify changes in chromosomes after exposure to environmental chemicals.

Discovering and Characterizing Cancer Predisposing Genes

The **Breast, Ovarian and Colorectal Cancer Family Registries** will expand 1) the epidemiologic and clinical follow-up of current participating high-risk families; 2) the molecular characterization of known colorectal, breast, and ovarian cancer susceptibility genes; and 3) the exploration of DNA

[2] Endocrine disruptors are synthetic or naturally occurring chemicals that affect the balance of hormonal functions.

Behavioral Factors and the Risk of Cancer

A number of studies have examined the relationship between cancer and a range of behavioral or lifestyle factors such as tobacco use, diet, physical activity, and alcohol consumption. Some researchers estimate that as many as 50 to 75 percent of cancer deaths in the United States are caused by behaviors or conditions that can be altered.

- **Cigarette smoking** is the most preventable cause of death in the United States. It leads to nearly one-third of the nation's cancer deaths and is the major cause of lung cancer incidence and mortality. Tobacco use can also cause cancers of the larynx, mouth, esophagus, pharynx, and bladder, and it plays a role in cancers of the pancreas, kidney, and cervix.
- **Obesity** increases the risk for several cancers including colon cancer, post-menopausal breast cancer, endometrial cancer, gastric cardia, and adenocarcinoma of the esophagus. People whose diets are rich in fruits and vegetables have a lower risk of getting cancers of the lung, mouth, pharynx, stomach, and colon.
- **Sedentary lifestyle** is a risk factor for colon and breast cancer, and physical activity has been linked to decreased incidence of cancer, including a 50 percent lower risk of getting colon cancer as well as to improved quality of life and recovery for cancer patients.
- **High alcohol intake** increases the risk of cancers of the mouth, esophagus, pharynx, larynx, and liver in men and women, and breast cancer in women.

Choosing healthy behaviors such as not smoking, maintaining a healthy weight, being physically active, eating a low-fat diet rich in fruits and vegetables, and avoiding too much alcohol can help to reduce cancer risk.

methylation and non-methylation related mismatch repair mechanisms and their relationship to cancer susceptibility. Studies will continue in breast, ovarian, and colon cancer to search for new susceptibility or modifier genes; to better understand the interactions of genetic markers with dietary and hormonal factors; and to develop new models for cancer risk prediction.

Family registries and collaborative groups are identifying susceptibility genes for prostate cancer as well as other familial cancer syndromes and discovering mutations of known genes for cancer site-specific susceptibility. NCI is also supporting new groups of investigators to use large registries of cancer prone families. For example, a large international genetic epidemiology consortium is studying melanoma.

Developing Tools for Gene Discovery and Characterization

NCI is developing a high throughput **Core Genotyping Facility** (CGF) capable of performing 40,000 genotypes every six weeks. The work will expand to 100,000 genotypes with the installation of an advanced Laboratory Information Management System. The CGF program has established partnerships with the National Human Genome Research Institute and several academic and commercial centers and is providing genomics support for the first Cohort Consortium study, described above.

The Centers for Disease Control and Prevention are funding three **Genomics and Public Health Centers** to develop methodologic standards specific to the collection and reporting of data from NCI-based population genetics research. This interagency collaboration is designed to more effectively move research results into clinical practice and public health.

The **Gail Model**, developed at NCI, is a statistical tool to help estimate a woman's risk of breast cancer based on a number of predisposing factors. A study of the reliability of mammographic densities was completed recently, and this characteristic has been found to be reliable enough to be formally included in the model.

Supporting Intervention Trials and Translational Research on Inherited Susceptibility

The **Cancer Genetics Network** (CGN) is a major NCI-supported infrastructure for studies of persons at high risk of cancer and for related translational research. CGN pilot studies combine existing and prospectively collected data to discover potentially important gene-environment interactions. The network collectively holds epidemiologic data on participants consistent with data collected by other NCI-supported consortia and registries allowing the information to be used either independently or in combination with other groups to explore gene-environment interactions.

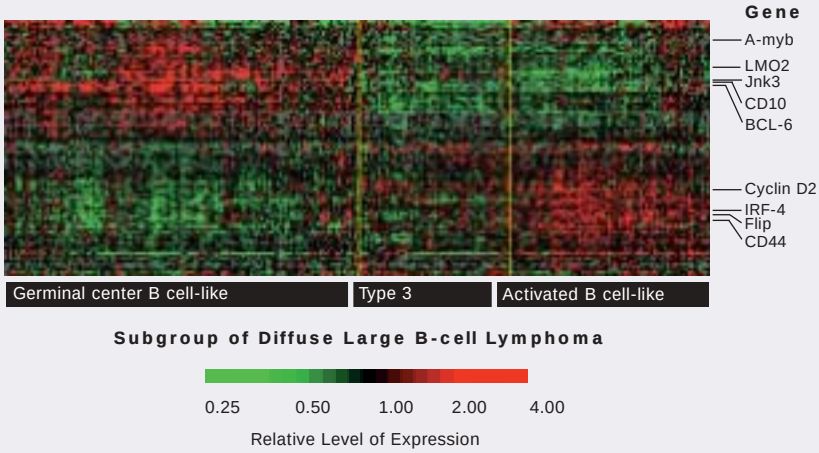
Genes and Proteins: Profiles of Hope

With advances in artificial intelligence and laboratory technology, cancer researchers are moving from studying a limited number of genes and proteins at a time to studying complex patterns of these molecules, using gene expression array (GEA) and proteomic technology. These patterns of genes and proteins can be displayed as easy-to-read, computer-generated tumor profiles that clinicians may one day use to:

- Diagnose cancer earlier than is now possible, perhaps with a simple blood test.
- Identify molecular targets for cancer prevention and treatment.
- Develop individualized therapies using targeted treatments.
- Monitor and predict response to therapy.

Recent advances in tumor profiling are pivotal and include the following:

- The Lymphoma/Leukemia Molecular Profiling Project, a consortium of researchers associated with the NCI Director's Challenge research initiative, are using GEA to predict clinical outcome of diffuse large-B cell lymphoma patients. These scientists are also researching tumor profiles of other lymphomas with the goal of classifying human lymphomas according to differing molecular features that can be used to select the best possible therapy for each subtype of this disease.
- NCI-supported researchers are using GEA to discriminate between subtypes of acute lymphoblastic leukemia (ALL). One rapid test yields diagnostic information that ordinarily takes weeks to gather. ALL tumor profiling also appears to be more accurate and information rich than traditional diagnostic methods, even identifying patients at greatest risk for relapse or secondary cancers. Similar tumor profiles are being developed for subtypes of lung cancers.
- Researchers in the Clinical Proteomics Program, recently launched jointly by NCI and the Food and Drug Administration, have developed a prototype blood test for the early detection of ovarian cancer. In preliminary clinical trials, the investigators correctly classified 100 percent of women known to have this cancer, and 97 percent of those known to be cancer-free. If successfully refined, this blood test will be invaluable for detecting this highly invasive disease in its earliest stages, when it can be successfully treated. Similar blood tests are being developed for prostate,[1] breast, and lung cancers.



Researchers used gene expression array to generate this tumor profile that discriminates between three subtypes of diffuse large-B-cell lymphoma (DLBCL). Each row represents a single gene. Each column shows the DLBCL expression profile from a single patient. If a gene is over active, its square shows up red. Less active genes show up green. It is the overall pattern of expression for each patient that can identify the disease sub-type and provide valuable prognostic information.

[1] See also page 9.

GOAL

Accelerate our progress in understanding the dynamic interaction between cancer cells and their microenvironment and our application of this knowledge to the detection, diagnosis, prevention, treatment, and control of all cancers.

Signatures of the Cancer Cell and Its Microenvironment

The Opportunity

Thirty years ago, cancer was a poorly understood and usually deadly disease. Today, we have a far better understanding of how cancer develops and progresses within the human body. Over the past three decades, scientists have determined that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change. These changes are unique molecular "signatures" and serve as signals of the presence of cancer. This more robust understanding of the genetic alterations that occur within a cancer cell has changed the course of cancer research and has fueled new approaches to prevention, detection, diagnosis, and treatment.

However, the cancer cell is only part of the story in cancer development. As a cancer cell grows within the elaborate architecture of the body's tissues and organs, it interacts with its surrounding environment. Mounting evidence now suggests that a dynamic interaction occurs between the cancer cell and its local and systemic microenvironment, with each profoundly influencing the behavior of the other. This "tumor microenvironment," is populated with a variety of different cell types, is rich in growth factors and enzymes, and includes parts of the blood and lymphatic systems. It conrtibutes to some of the most destructive characteristics of cancer cells and permits a tumor to grow and spread. The microenvironment can also influence the access of therapeutic agents to tumor cells, the body's processing of treatment agents, and the development of resistance to cancer treatments. Although the cells in the microenvironment may not be genetically altered, their behavior can be changed through interactions with tumor cells. Physicians now realize that they confront a tumor entity that consists of malignant cells combined with their host tumor environment when treating a cancer patient. The cancer cells and their surrounding environment both need to be fully characterized in order to understand how cancer grows in the body, and both need to be considered when developing new interventions to fight it.

Six years ago, NCI established the "Defining the Signatures of Cancer Cells" Extraordinary Opportunity to promote research aimed at identifying and characterizing the full compendium of signature changes that occur within cancer cells. Now we are expanding our efforts to consider how the interaction of the cancer cell and microenvironment permits, and even encourages, tumor development. Scientists pursuing this promising new scientific opportunity will read not only the signatures of cancer cells but also signatures of seemingly normal cells within the tumor microenvironment, and signatures that reflect changes that occur as cancer cells interact with the host microenvironment. NCI's long-range goal is to extend signatures research to characterize the interaction among a tumor, its microenvironment, and the entire body. All of these signatures of cancer provide important clues for understanding cancer development, detection, diagnosis, and prognosis and are potential targets for preventive or therapeutic interventions.

Progress in Pursuit of Our Goal

Through a variety of ambitious initiatives, scientists studying the signatures of cancer are making important progress in identifying and characterizing both the signatures of premalignant and malignant cells as well as cells within the tumor microenvironment and validating these unique signatures as markers for early detection and diagnosis.

The **Cancer Genome Anatomy Project** (CGAP), launched six years ago, is a critical vehicle for coordinating data and reagents that will support advances in molecular detection and diagnosis. The central goal of this project is to provide a complete picture of all the major molecular changes that occur

Signatures of the Cancer Cell and Its Microenvironment

G O A L

Accelerate our progress in understanding the dynamic interaction between cancer cells and their microenvironment and our application of this knowledge to the detection, diagnosis, prevention, treatment, and control of all cancers.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Define the molecular signatures of cells in the cancer microenvironment at various points during initiation and progression of cancer. Compare the molecular signatures of stromal and cancer cells during development and aging. **$10.00 M**

- Initiate a Consortium for Microenvironment of Tumors to define the molecular signatures of cancer cells and cells in the microenvironment. Establish a national core facility to facilitate the analysis of normal and cancerous cell samples for signature profiling studies. $4.00 M
- Develop a database of the molecular signature profiles of cells in the microenvironment and make these data readily available to the research community. $1.00 M
- Expand the Unconventional Innovations Program (UIP) to permit an increased focus on nanoparticles, molecular beacons, and high-resolution sensors and their use in cancer signature detection, targeting, and treatment. $2.00 M
- Expand the Innovative Molecular Analysis Technologies Program (IMAT) to enable development of micro- and nanotechnology tools to detect molecular signatures of cancer and surrounding cells. Facilitate collaborations that will assist in translating IMAT technology into tools that can be used in clinical practice. $3.00 M

2. Define the dynamic communications among cancer cells, surrounding cells, and immune cells that control or promote tumor growth. Characterize the interaction between the immune system and the cancer cell during cancer initiation and progression. **$ 7.00 M**

- Fund studies focused on identifying the factors used by cancer cells to activate cells in the tumor microenvironment, which in turn support tumor growth and progression. $1.50 M
- Support studies to identify the origin of the cells and factors that comprise the tumor microenvironment. $1.50 M
- Develop organotypic culture systems that accurately model the interaction between the cancer cell and the tumor microenvironment in living systems. Make these systems readily accessible to the research community. $2.00 M
- Develop technologies to enable researchers to assemble selected cell populations into tissues and engraft these “assembled” tissues into mice to observe and monitor the subsequent biological behavior of the grafted tissue. $2.00 M

3. Support new approaches to provide the research community with rapid access to validated reagents. **$ 6.00 M**

- Establish a repository for antibodies, cell lines, animal models, and tissues that relate to cells in the microenvironment. $1.00 M
- Establish a database that includes comparisons of cellular interactions between cancer and surrounding cells in animal models to those in humans. $1.00 M
- Expand the Tissue Array Research Program (TARP) to include tissue microarrays of normal and cancerous tissues that are enriched for tissue from the tumor microenvironment. $2.00 M
- Expand the Clinical Proteomics Program to identify proteins and proteomic signatures in human cancer microdissected tissue samples (normal epithelium, premalignant lesions, adjacent tissue, and invasive cancer). $2.00 M

4. Establish a spectrum of educational and communication initiatives involving scientists across various disciplines and with a broad range of expertise to enable progress in understanding the role of stromal cell interactions in cancer development. **$ 4.00 M**

- Encourage multi- and transdisciplinary investigations by establishing a new funding mechanism to allow co-investigators from different scientific fields to submit a collaborative grant application. $2.00 M
- Establish national trans-disciplinary training centers that will develop training curricula for students and established investigators and facilitate the development of novel studies in understanding the role of cellular interactions in cancer development. $2.00 M

5. Apply knowledge of cellular interactions in cancer development, derived from profiling studies exploring cell-microenvironment interactions to create targeted interventions. **$12.00 M**

- Initiate a Rapid Access to Intervention Development program to efficiently develop new drugs that target cells in the microenvironment and move them into clinical use. $2.00 M
- Provide supplemental funding to NCI-funded investigators to develop new "targeted" reagents, including small molecules, RNAi, and antibodies. $5.00 M
- Fund functional and molecular imaging studies to visualize the physiologic, cellular, and molecular processes in living tissues. These studies should focus on (1) identifying the subtle and important early changes in the molecular biology of tumors and the microenvironment, as tumors become malignant and (2) monitoring the effects of therapy on tumor cells and the tumor microenvironment. $5.00 M

Management and Support **$ 2.20 M**

Total **$41.20 M**

during cancer development. All CGAP data and resources are publicly accessible to the biomedical research community, enabling researchers to find "in silico"[1] answers to biological questions in a fraction of the time it once took in the lab.

- Through the **Tumor Gene Index**, CGAP has now generated more than 8 million gene tags (ESTs) from a wide variety of tumor types and their normal counterparts. Scientists are incorporating these ESTs into the design of microarrays and other technologies that will be used to classify tumors according to their molecular features. These molecular classification strategies hold the potential to improve cancer prevention, early detection, diagnosis, and treatment.
- CGAP's **Cancer Chromosome Aberration Project** was established to generate a genetic map that defines distinct chromosomal alterations associated with cancer. In 2002, investigators accomplished this initial goal, a milestone achievement in cancer research.
- Full-length complimentary DNA clones are important tools for defining the sequence and function of genes expressed in human cells. Generating these clones, however, requires a considerable investment of an investigator's time and funds. The **NIH Mammalian Gene Collection**, for which CGAP plays a leadership role, was created to generate individual full length human and mouse DNA clones for more rigorous study of individual genes, their protein products, and the role they play in human genes. The MGC has now identified potential full-length clones for more than 20,000 human genes and 11,000 mouse genes.
- CGAP's **Genetic Annotation Initiative** focuses on exploring and applying technology to identify and characterize sequence variations, known as genetic polymorphisms, in genes important in cancer. A genetic polymorphism, which can affect a gene's function, can arise when a mutation causes a change in even a single nucleotide of the DNA. Single nucleotide polymorphisms (SNPs) are important markers for cancer risk-related genes and also can be used to understand difference in vulnerability to cancer among individuals in a population. The CGAP SNP500 Cancer project, a new GAI effort, will sequence and make available to researchers 102 samples for known or newly discovered SNPs of immediate importance to molecular epidemiology studies in cancer.

Innovations in laboratory technology and artificial intelligence are allowing scientists to move beyond studying genes or proteins one or two at a time, to studying the patterns (or profiles) of these molecules in normal, pre-cancerous, and cancerous cells. In 2001, NCI and the Food and Drug Administration launched the **Clinical Proteomics Program** (CPP) to apply advances in proteomics — the study of protein expression and function — directly to patient care. CPP investigators are pursuing a number of projects to achieve earlier detection of cancer through minimally invasive testing, individualized diagnosis and treatment strategies, determination of risks and benefits of treatments in the laboratory before use on patients, and enhanced understanding of tumors at the protein level, leading to molecular targeted therapies for cancer.

NCI's **Biomedical Proteomics Program** is supporting these efforts through its Mass Spectrometry Center. The center is a newly developed state-of-the-art facility that employs several powerful new technologies to cleanly separate proteins and characterize their activities in cancer cells. Proteomic studies will also be aided by a technology recently developed by investigators funded through the **Innovative Molecular Analysis Technologies** program. This new technology combines the use of a laser (to release proteins directly from the surface of tissue sections) with mass spectrometry to accurately identify and localize proteins in cells and tissues. The technology, which has successfully imaged the location of proteins in tissue sections from human glioblastoma, prostate, and colon tumors, should provide new insights into molecular interactions within a cell. It also promises to be a valuable tool in the search for detection, diagnostic, and treatment markers.

The **Tissue Array Research Program** (TARP), a collaborative effort between the National Human Genome Research Institute and NCI, is a valuable tool for testing interesting genes discovered in profiling studies. The TARP laboratory has produced more than 4,000 tissue microarray slides containing a variety of tumor and normal tissue samples. In a joint effort with the CPP, the TARP laboratory has also developed a cost-effective and user-friendly "cryo-array" platform that can be used to build arrays from very small tumor samples.

[1] "In silico" techniques allow activities currently carried out *in vitro* or *in vivo* to be transferred to the computer.

The Early Detection Research Network (EDRN) is a comprehensive, collaborative program that merges genetics with proteomics to provide a systematic view of how the molecular signatures of specific cancers can be used as unique, identifying markers. Through EDRN, NCI has created a national research infrastructure in which researchers from multiple institutions work together to identify, develop, and validate early detection markers. EDRN scientists have already discovered a number of novel biomarkers for breast, colon, lung, and prostate cancer and continue to pursue a variety of other promising investigations.

NCI and EDRN scientists are jointly developing a proteomic profile for early detection of breast cancer based on the discovery of a protein profile in blood and breast fluid samples that distinguishes women without breast cancer from women with early, curable breast tumors. Researchers plan to test the protein profile defined by this study to determine its use as a marker for early detection of breast cancer. The same proteomics technology is also being tested for its applicability to ovarian, prostate, and lung cancer detection. In a preliminary trial of the technology to detect ovarian cancer, investigators were able to correctly identify ovarian cancer in all of 60 women with the disease. Out of 66 patients known not to have cancer, 63 (or 97 percent) were correctly identified as cancer free. Although the accuracy of this test must be improved before it can be used to screen women in the general population, these are exceptionally promising preliminary results.

Through the **Director's Challenge: Toward a Molecular Classification of Tumors** initiative, investigators are developing profiles of molecular changes in human tumors using DNA, RNA, or protein-based analysis strategies to complement the current tumor classifications that are based on microscopic features. Three groups of Director's Challenge investigators — using different experimental approaches — have identified expression profiles that differentiate early lung adenocarcinomas with a poor prognosis from adenocarcinomas that respond favorably to treatment. Although these tumors have different clinical behaviors, they cannot be distinguished from each other by their microscopic appearance. The ability to differentiate these tumors may help to distinguish between patients who can be cured by surgery alone from those who may benefit from more aggressive, or eventually, targeted interventions. The profiles may also reveal previously unknown molecular changes that can be tested as potential targets of new treatments. Director's Challenge investigators have also reported new classification schemes for breast cancer and are working to develop new classification schemes in many other tumor sites. These results demonstrate the power of comprehensive molecular analyses to provide information that one day may guide a physician's decision about the treatment course for individual patients.

The **Mouse Models of Human Cancers Consortium** (MMHCC), a large initiative focused on developing and making available to researchers validated mouse models that mimic human cancers, is a vital part of cancer signatures research. With these models, scientists can identify and characterize cancer-associated molecular changes in complete organisms. Recently, several studies using MMHCC-developed prostate cancer mouse models demonstrated that growth factor signaling between the cancer and surrounding cells contributes to tumor progression. Based on this information, a group of researchers have engineered a new animal model lacking a specific growth factor in the tumor microenvironment to explore how growth factor loss may affect tumor progression. They also are studying mice engineered to over-express growth factors in either tumor or microenvironment cells to define the impact of these factors on tumor initiation. Finally, they are using mice with an intact signal system to design strategies to interrupt the signals as potential therapy.

The **Program for the Assessment of Clinical Cancer Tests** (PACCT) facilitates the translation of new knowledge about cancer and new technologies into clinical practice. A Strategy Group, which guides the PACCT, has developed statistical designs for trials of markers that predict response to particular therapies. The Group has also developed an algorithm for developing new prognostic and predictive tests. Working groups will identify promising markers for node-negative breast and colon cancer and determine what steps need to be taken, according to the algorithm, to move these markers into clinical practice. In addition, a PACCT funding initiative has been developed to facilitate clinical trials to evaluate melanocyte tumor classification, molecular predictors of oral cancer, and the use of nipple aspirate to assess breast cancer risk.

G O A L

Facilitate the expanded exploration of the causes of cancer and the discovery and development of agents that specifically "target" these causes to prevent and treat cancer.

Molecular Targets of Prevention and Treatment

The Opportunity

Recent advances in deciphering the human genome have launched an exciting new era in biomedical research with tremendous potential for cancer prevention, diagnosis, and treatment. New drugs can now be designed to target specific molecular features characteristic of cancer cells, including genetic mutations, factors causing changes in gene expression,[1] structural changes in the proteins that are products of mutated genes, and alterations in signaling pathways.[2] Molecularly targeted interventions result from the integration of multiple research disciplines and can be classified into five general molecularly targeted strategies that will guide future research. (See figure below.)

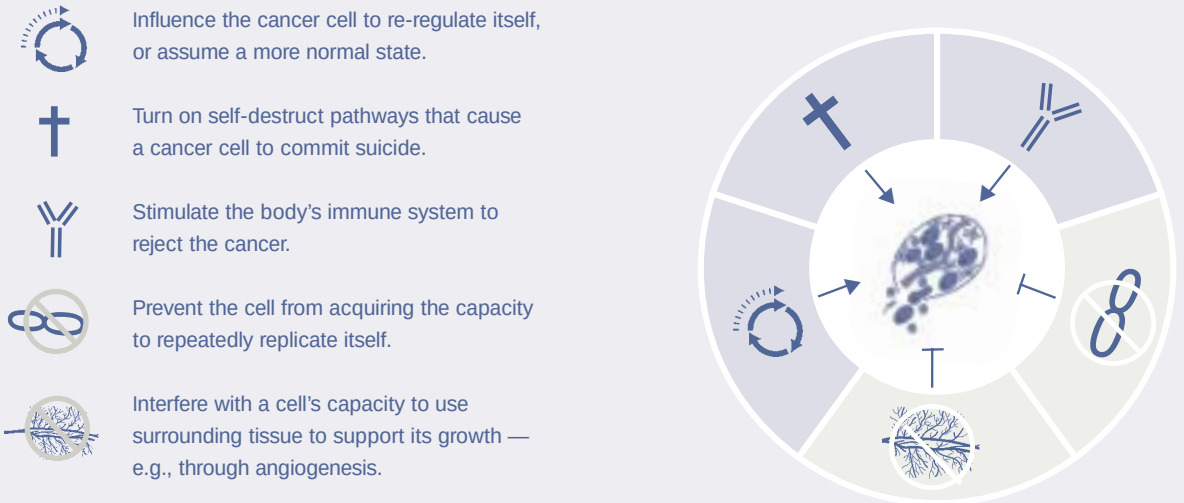
Drugs developed using past paradigms attack both cancerous and healthy cells, often causing devastating short- and long-term side effects. Moreover, individual patient responses to conventional agents vary, even in cases where cancers appear to be identical. Molecularly targeted therapies promise to be more selective, drastically reducing the incidence of side effects in patients. New diagnostic tools will permit clinicians to more precisely identify those patients who are most likely to benefit from a given therapeutic agent. Drugs developed to target one type of cancer are often found to be effective against other cancers as well. We foresee a day when the treatment for each patient's cancer will be individualized based on the unique set of molecular characteristics expressed by his or her tumor.

Progress in Pursuit of Our Goal

NCI is advancing the identification of molecular targets and targeted drug discovery through a number of exciting initiatives. Several of these efforts address needs identified by Progress Review Groups, expert panels who assess research requirements for specific types of cancer.

[1] A gene is said to be "expressed" when the cell uses its genetic information to produce protein.
[2] "Signaling pathways" are molecular interactions that begin when a cell receives a signal, such as a protein binding to a receptor, from outside of itself.

Research Avenues for Molecular Targeting



Identifying and Validating Molecular Targets

Through the **Molecular Target Drug Discovery** program, investigators identify and validate potential sites that can be exploited for cancer prevention and therapy, and develop tests to determine how effectively potential agents work on these targets. Other NCI programs support the development of resources for exploiting molecular targets. The **Molecular Targets Laboratory** capitalizes on the opportunities emerging from advances in genomics, molecular biology, combinatorial chemistry, informatics, and imaging, to create a resource of biological assays and compounds used to study molecular targets. The **Mouse Models of Human Cancers Consortium** is a collaborative program designed to derive and characterize mouse models of human cancers, and to generate resources, information, and methodologies to apply in cancer research. The Consortium expects to make available to researchers up to 30 new mouse models each year, and it is developing partnerships with pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds identified by consortium members.[3]

Evaluating the Therapeutic Potential of Compounds

NCI-supported chemists and biologists are collaborating to create libraries of synthetic, biological, and natural compounds to identify agents that can hit targets. The next step is to evaluate their therapeutic potential in molecular target assays. **The National Cooperative Drug Discovery Groups** program supports innovative, multi-disciplinary, parallel approaches for discovery of new anti-cancer treatments. Thirteen groups are progressing in a variety of areas. One group is developing novel vaccines targeting a receptor called Her2/neu that is over-expressed in up to 50 percent of breast cancers and is associated with metastatic disease and poor prognosis. In **Biology-Chemistry Centers**, interdisciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of structurally diverse chemical compounds with potential anti-cancer effects. Using "smart" assays, scientists screen the compounds to identify those that will interact with cancer-specific molecular targets. The six teams funded through this initiative have screened hundreds of thousands of compounds for anti-cancer activity. Promising compounds include inhibitors of new blood vessel formation (angiogenesis), essential for tumor growth; a molecule that binds to growth factors and inhibits tumor growth; and a novel cell cycle inhibitor that could affect many cancers. **Rapid Access to NCI Discovery Resources** is a new program that expedites the development of drug research capabilities in academic institutions by assisting in the development of high-throughput laboratory assays to screen large numbers of promising chemicals. One recently funded project will target antibodies to angiogenin, an enzyme that can increase blood vessel growth in tumors.

To expedite drug discovery, NCI is providing sample sets of more than 140,000 synthetic chemicals; 80,000 natural products extracted from plants and marine organisms; and other biological materials to investigators who might have discovered potential targets. More than 60 research groups engaged in targeted cancer research have been supplied with these sets. Sample sets from the repository are helping NCI's **Chemistry and Biology Group** with research on a novel cell cycle inhibitor.

Translating Promising Target-Directed Compounds into Drugs for Human Use

This is an exacting task that requires very specific, interrelated activities. NCI is supporting this critical arm of intervention development through a variety of initiatives. The **Rapid Access to Prevention Intervention Development** program expedites preclinical and early clinical drug development of investigational agents, with the potential to prevent, reverse, or delay carcinogenesis, by making the preclinical and early clinical drug development contract resources of NCI available to academic investigators. Through 17 currently funded projects, NCI supports clinical trials of mechanistically targeted agents to examine the effects of various chemopreventive agents on molecular targets. **The Rapid Access to Intervention Development** (RAID) program provides preclinical drug development resources to academic institutions in 62 current projects. Three interventions developed through RAID are now being tested in clinical trials. One intervention is a novel gene therapy approach that delivers a pair of therapeutic "suicide genes" to prostate tumors, rendering malignant cells sensitive to specific drugs and radiation. As many as six additional agents, targeting pediatric neuroblastoma, pancreatic cancer, and tumors expressing a variant epidermal growth factor receptor, will be in clinical trials by the end of FY 2002.[4] NCI's **Drug Development Group** provides

[3] emice.nci.nih.gov
[4] dtp.nci.nih.gov/docs/raid/raid_index.html

Molecular Targets of Prevention and Treatment

GOAL

Facilitate the expanded exploration of the causes of cancer and the discovery and development of agents that specifically "target" these causes to prevent and treat cancer.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Identify, characterize, and validate the combinations of deregulated cellular proteins and pathways that cause cancer in pre-cancerous and cancerous cells. — **$ 6.00 M**

- Through the Molecular Target Drug Discovery and other grant mechanisms, expand research to identify cellular targets and discover related anti-cancer agents. Provide screening assistance and informatics management. $6.00 M

2. Determine the cancer-causing deregulated pathways that can be targeted by treatment or prevention agents. — **$ 7.00 M**

- Amplify support for the Molecular Target Laboratory to bolster the systematic search for new preventive and therapeutic agents: 1) develop assays to identify possible treatments for cancer, and 2) acquire large libraries of natural and synthetic compounds. $5.00 M
- Support the Mouse Models of Human Cancers Consortium. $2.00 M

3. Provide the infrastructure for researchers to develop assays to test large numbers of potential drugs against validated targets [e.g., deregulated proteins and pathways]. — **$16.00 M**

- Expand support for the National Cooperative Drug Discovery Groups and encourage "partnering" arrangements with large and small pharmaceutical companies. $5.00 M
- Expand the availability of NCI discovery resources to academic laboratories through the Rapid Access to NCI Discovery Resources program. $1.00 M
- Support the creation of novel chemical compound libraries for molecular target assays through new Small Business Innovation Research initiatives. $4.00 M
- Develop a translational research program to closely link molecular imaging, cancer signatures, and molecular targets. These concurrent studies will couple the image to the biology to aid in credentialing new molecular targets. $3.00 M
- Develop screening assays to test candidates for probes and inhibitors of molecular targets and characterize and validate compounds that hit the targets through the intramural Molecular Targets Development Program. Support the isolation, purification, and characterization of individual components of natural product extracts. $1.00 M
- Develop a clinical proteomics initiative to use laser capture microdissection of human tissue specimens and to develop new laboratory tools for clinical proteomic applications in human cancer and drug toxicity detection. $2.00 M

4. Facilitate the steps necessary to turn a target-specific lead compound into a clinical agent. — **$ 9.00 M**

- Expand support for the Rapid Access to Intervention Development program. $3.00 M
- Increase funding to the Rapid Access to Prevention Intervention Development program to develop agents from the laboratory through clinical trials of efficacy. $1.00 M

- Support the development of novel methods of drug formulation and drug delivery through new Small Business Innovation Research initiatives. $2.00 M
- Expand assistance to small business drug research and development through the Flexible System to Advance Innovative Research program. $3.00 M

5. Investigate the use of novel combinations of radiation therapy with molecular therapeutics. **$ 0.50 M**

- Support individual investigators and industry to develop treatment programs using new agents with radiation therapy. $0.50 M

6. Fund Clinical Trials Networks that will take drug candidates into human trials and determine if the drug affects the intended target and the progression of the cancer. **$ 2.00 M**

- Widen support for the Interdisciplinary Research Teams for Molecular Target Assessment. $2.00 M

7. Utilize current technologies to make the next generation of cancer vaccines more effective in inducing anti-cancer responses, either before or during the use of other therapies. Support vaccine development and clinical trials of new vaccines. **$ 8.30 M**

- Develop more potent vaccines by integrating various approaches and translating them into optimal therapies for human cancer. $1.50 M
- Generate specialized cell types, such as dendritic cells, for use as vaccines. $0.70 M
- Create animal models that both develop spontaneous tumors later in life, to allow time for appropriate vaccination protocols, and express tumor-associated antigens similar to those in humans. $0.30 M
- Establish laboratories to analyze new gene products for potential use in cancer vaccines and to develop methods to increase immunogenicity. $0.50 M
- Expedite the development of clinical trials to assess the efficacy of new vaccines for the treatment of colorectal, prostate, breast, lung, bladder, pancreatic, and head and neck carcinomas; myeloma, lymphoma, and melanoma; and other tumor types.
  - — Develop new funding mechanisms to support clinical trials. $2.50 M
  - — Obtain and make available samples of immune cells and tumor tissue from patients for immunoassay testing. $0.50 M
- Establish centralized immunoassay laboratories to analyze patient immune responses both prior to and during vaccine clinical trials. Supplement existing laboratories to develop immunoassays to select good candidates for vaccine therapy. $0.50 M
- Develop and conduct clinical trials to test the efficacy of using cancer vaccines in combination with existing therapies including chemotherapy, hormonal therapy, or local radiotherapy. $1.50 M
- Develop new surrogate markers of vaccine efficacy and tests revealing the presence of bloodborne tumor cells that express tumor antigen genes. $0.30 M

Management and Support **$ 6.00 M**

Total **$54.80 M**

support for academic and corporate-derived compounds when NCI is responsible for conducting and monitoring the drug's clinical development. For more than 15 years, researchers have attempted to design cancer therapies to avoid toxicities associated with standard chemotherapeutic agents. BL22, an immunotoxin that specifically targets hairy cell leukemia (HCL), originated in an intramural NCI laboratory and was developed through NCI's biologicals production facility. It is now showing promising results in a Phase I trial: 11 of 16 patients with chemotherapy-resistant HCL have shown complete remission, lasting up to 18 months, mostly without major side effects. The **Flexible System to Advance Innovative Research** provides funds to small businesses to develop cancer therapeutic and prevention agents from basic discovery to clinical trials. One of these grants supported development of an immune modulating agent called A-007, already in Phase I clinical trials. This agent has been approved for Phase II trials to test its efficacy in treating cervical cancer. The **Radiation Modifier Evaluation Module** program will serve individual investigators and industry in the design and development of treatment programs using novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. This integration is a high priority of NCI's Intramural Program because new anticancer agents may ultimately be used in combination with radiation therapy.

Developing Clinical Trials Programs To Study New Molecular Target Agents

As part of large-scale prevention trials, NCI supports supplemental studies and specimen repositories aimed at answering a variety of mechanistic and molecular questions. For example, in the **Selenium and Vitamin E Cancer Prevention Trial**, scientists will assess the molecular genetics of cancer risk and associations between diet and cancer. In the **Breast Cancer Prevention Trial**, the **Study of Tamoxifen and Raloxifene** focused on the estrogen receptor as a key to breast cancer risk.

NCI is fostering teams of interdisciplinary scientists through the **Interdisciplinary Research Teams for Molecular Target Assessment**. These teams study critical biological processes to uncover high priority targets for cancer prevention or treatment and drug discovery. The first set of applications, focusing on angiogenesis, tumor proliferation, tumor vaccines, and structure of tumor chromosomes, was funded in 2001.

Fostering Interdisciplinary Collaborations through NCI Intramural Programs

NCI's **Center for Cancer Research**, which coordinates all intramural basic and clinical research, expedites rapid and efficient translation of basic scientific advances into new tools, reagents, and molecularly targeted leads. Major priorities of the Center include fostering interdisciplinary collaborations between basic researchers and clinical investigators and training postdoctoral fellows to function in this new research environment. To this end, NCI has formed the **Molecular Targets Faculty,** composed of scientists from diverse laboratories and branches working together cooperatively as part of the intramural **Molecular Targets Development Program**. The Program also promotes collaborations with various academic and pharmaceutical partners and is designed to facilitate the discovery of compounds that can serve as probes for functional genomics, proteomics, molecular target validation, or as candidates for drug development.

Recognizing the importance of anti-cancer vaccines in prevention and treatment, NCI has established the **Center for Cancer Research Vaccine Initiative**, a consortium of multidisciplinary scientists, consisting of expert clinicians and industrial representatives. This consortium has spearheaded the development of new, more sophisticated recombinant vaccines that are now in the clinic and others that will enter the clinic shortly.[5] The potential of proteomics to further cancer research is being exploited by two other programs. The **Biomedical Proteomics Program** provides NCI investigators with the most powerful analytical approaches available to further the understanding of the molecular mechanisms underlying carcinogenesis and tumor progression and works hand in hand with the NCI **Clinical Proteomics Program** to identify proteins and pathways important in human cancers.

[5] See page 16 for more information on the Vaccine Initiative.

G O A L

Accelerate discovery and development of imaging methods, biosensors, and minimally invasive image-guided therapies to predict clinical course and guide and predict response to interventions.

Cancer Imaging and Molecular Sensing

The Opportunity

Over the last quarter century, investment in cancer imaging has dramatically improved the quality of patient care by making it possible to detect tumors much earlier when they are easier to treat and by permitting more precise therapy or surgery. New imaging techniques can be used to determine, in real time, if a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs. Imaging supports various tumor-destroying approaches (chemicals, radiation, gene therapy, heat, and cold) to minimize surgical trauma and damage to healthy tissue, shorten recovery time, and reduce healthcare costs. Molecular or "functional" imaging[1] of the physiological, cellular, or molecular processes in living tissue can sometimes allow physicians to monitor their patients' progress and response to therapy without the need for biopsies.

Indeed, more imaging resources are devoted to the study and treatment of cancer than to any other disease and, in many ways, the needs of cancer research and treatment drive the direction of imaging research. As we learn more about the molecular basis for cancer, this level of sustained investment in cancer imaging becomes even more necessary and productive. For example, micro-imaging technologies are needed to fully utilize the increasing number of mouse models of human cancer to uncover the genetic basis of specific tumors. We need to develop functional imaging to study how newly discovered defects in genes and proteins interact to cause cancer. Recent discoveries in cancer signature and molecular therapeutic research demand new ways to assess the effectiveness of molecularly targeted treatments in clinical trial settings.

At the same time, we must invest in applying the new technologies emerging from the study of nanoscience[2] that promise to give biomedical researchers and healthcare providers even more options for detecting and monitoring biologic events in cancer. Researchers are designing molecular *biosensors* to be injected into the bloodstream to seek out and destroy cancer cells. These biosensors, about 10,000 times smaller than the head of a pin, will also allow physicians to image the cancer and follow the patient's response to therapy — all with minimal side effects and little disruption of healthy tissue.

NCI has a unique opportunity to further improve cancer imaging and molecular sensing technologies to ensure earlier and more accurate diagnoses for cancer patients, reduce the number of invasive interventions, guide individualized therapies, and improve monitoring of patient response to treatment. With additional investment in research and development, significant advances in these areas will increasingly save and improve lives.

Progress in Pursuit of Our Goal

NCI's investment in developing better imaging technologies for both cancer research and clinical practice are tangibly impacting patient's lives.

Developing Better Imaging Technologies and Techniques

NCI has played a major role in fostering **functional imaging** through initiatives such as ***In Vivo* Cellular and Molecular Imaging Centers** (ICMICs). With five Centers established as of 2002, each ICMIC brings together experts from diverse scientific and technological backgrounds to conduct multidisciplinary research on cellular and molecular imaging in cancer.

[1] Molecular imaging techniques do not actually reveal molecules themselves, but they detect signals that indicate the presence of biochemical activity and changes, such as cell growth or death. Thus, molecular imaging is often described as "functional," because the processes being imaged are active and constantly changing.

[2] Nanoscience is the study of objects and phenomena on extremely small scales.

Cancer Imaging and Molecular Sensing

GOAL

Stimulate and accelerate discovery and development of imaging methods and biosensors to identify the biological and molecular properties of precancerous or cancerous cells that will predict clinical course and response to interventions. Advance the development and implementation of minimally invasive image-guided therapies.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Expand the discovery, design, and development of novel imaging agents and devices. **$34.80 M**

- Establish two additional *In Vivo* Cellular and Molecular Imaging Centers (ICMICs) to foster multidisciplinary research in this area of study. $4.00 M
- Increase the number of imaging agents supported by the Development of Clinical Imaging Drugs and Enhancers program from three to five per year. $4.00 M
- Increase collaborations between Small Animal Imaging Resource Programs (SAIRPs) and other NCI programs such as the Mouse Models of Human Cancers Consortium (MMHCC). $2.00 M
- Provide 10 supplements to SAIRPs to upgrade to state-of-the-art imaging devices. $5.00 M
- Speed the development of imaging agents by funding supplements to grantees in a variety of NCI programs that perform research on molecular imaging. $2.00 M
- Fund research supplements to investigators to make their imaging discoveries such as contrast agents, assays, devices, and software available to others. Establish a repository of imaging agents for investigators at the National Cancer Institute at Frederick. $3.50 M
- Establish data banks of standardized digital image or spectroscopy data (such as virtual colonoscopy, digital mammography, digital chest imaging, and optical spectroscopy) associated with known clinical outcomes as a research resource. Expand the NCI-funded, publicly available, Molecular Imaging Database of imaging agents. $5.30 M
- Fund six to eight grants to develop and test image processing and analysis algorithms (artificial intelligence). $2.00 M
- Fund four grants (RFA) to stimulate the development of combined modality devices. $4.00 M
- Accelerate commercialization of imaging discoveries by fostering academic-industry collaborations with funding supplements similar to the National Science Foundation Grant Opportunities for Academic Liaison with Industry (GOALI) program. $1.50M
- Fund four grants to develop standardized image acquisition and image processing protocols for calculating quantitative endpoints for clinical trials. $1.50 M

2. Increase clinical trials of imaging methods and technologies. **$14.00 M**

- Initiate clinical studies to evaluate: computed tomographic colonography (virtual colonoscopy) compared to endoscopic colonoscopy for early detection of colon cancer and polyps in a large multi-institutional setting; magnetic resonance (MR) spectroscopy for the early detection and assessment of prostate cancer; MR imaging and ultrasound for early detection of breast cancer; and positron emission tomography for monitoring tumor response to therapy. $10.00 M

- Support correlative imaging studies, such as monitoring response to therapy, with 10 funding supplements to Clinical Trials Cooperative Groups. $4.00 M
- Fund a workshop to talk with industrial and academic leaders about applying the latest imaging technology to lung cancer detection.

3. Integrate molecular and functional imaging methods into therapeutic clinical trials. **$12.20 M**

- Increase the contract support for early clinical trials of imaging agents (safety and efficacy studies) from 6 to 10 trials per year. $2.00 M
- Provide imaging expertise to clinical trials by funding supplements or grants for 10 to 15 imaging cores within NCI-funded Cancer Centers and support expert panels to develop consensus criteria for using imaging results as endpoints in clinical trials. $4.20 M
- Provide funding for dedicated imaging equipment (infrastructure) for clinical trials. $5.00 M
- Expand a contract program to validate imaging methodologies in pre-clinical testing of new drugs. $1.00 M

4. Accelerate the development and clinical testing of image-guided interventions. **$12.00 M**

- Use 6 to 10 funding supplements to enhance programs such as the SPOREs for image-guided therapy research that emphasizes a problem-solving, organ-specific approach and promotes interactions between clinicians and bioengineers. $3.00 M
- Increase collaborations between the American College of Radiology Imaging Network and other NCI-funded Clinical Trials Cooperative Groups for testing promising, minimally invasive, image-guided interventions with 4 to 6 funding supplements. $2.00 M
- Support 6 grants to develop the tools and infrastructure to incorporate functional and molecular imaging into radiation therapy planning. $2.00 M
- Fund an initiative of 10 grants (RFA) to stimulate the development and systems integration of hardware and software tools and for image-guided delivery of therapies to solid tumors. $5.00 M

5. Stimulate research on components and systems integration of devices for *in vivo* molecular sensing (biosensors). **$ 4.00 M**

- Fund 6 to 8 supplements to investigators in the Innovative Molecular Analysis Technology, Unconventional Innovation Program, or NCI-NASA collaboration to develop biosensors or components of biosensors for *in vivo* use. $2.00 M
- Promote research on biosensor systems integration by funding a Center for Biosensors in Oncology, based on the National Science Foundation Engineering Research Center model. $2.00 M

Management and Support **$ 1.70 M**

Total **$78.70 M**

NCI is providing support for the planning of another 14 potential ICMIC sites. For highlights of one ICMIC team effort, see the sidebar below.

NCI's **Development of Clinical Imaging Drugs and Enhancers** (DCIDE) program is continuing to foster the development of new imaging contrast agents and molecular probes to improve the diagnosis and treatment of cancer. By its second year, DCIDE will be developing as many as seven imaging agents or probes designed to measure blood vessel formation and cell death, evaluate cell growth, and enhance visualization of prostate and other cancers.

Several of NCI's Progress Review Groups have stressed the need for publicly available imaging databases to support optimal growth in imaging research and technology. The NCI-supported **Molecular Imaging Database**, expected to be released in 2002, will help researchers develop new imaging agents and help clinicians find existing agents for imaging specific cancers.
By early 2003, NCI's **Lung Imaging Database Consortium** will provide databanks of standardized digital image data from cancer patients, together with clinical outcome information, a resource much requested by researchers.

Researchers of the Mouse Models of Human Cancers Consortium (MMHCC) are developing **inventive imaging modalities for use in preclinical studies**. One group is using MRI to learn how to deliver anti-tumor therapy to the brain using neural stem cells. Other researchers use a unique micro-computed tomography imaging (micro-CT) contrast agent to visualize metastatic tumors in the livers of mice with invasive colon cancer. This team developed a second agent to track metastases in other organs throughout the mouse.

Bringing Advances in Imaging to Cancer Care

NCI is supporting **clinical trial research** to move promising imaging advances from discovery and development to clinical use. New cancer imaging technologies and techniques are often evaluated through one of NCI's clinical trials cooperative groups. These groups are networks of healthcare professionals affiliated with medical schools, teaching hospitals, and community-based cancer treatment centers. For example, the **American College of Radiology Imaging Network** (ACRIN) recently completed a study to determine whether computed tomography (CT) scanning — a technique sometimes known as "virtual colonoscopy" — is sufficiently reliable for colon cancer screening to warrant further study. Based on their promising results, a large-scale trial will follow this study.

Other ACRIN efforts are underway to determine:

- Whether combined Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopic Imaging can be used to accurately localize and diagnose prostate cancer.
- Whether CT scanning can be used to reliably measure tumor volume of supraglottic cancer.
- How the drug Gleevec™ impacts the biology of Gastrointestinal Stromal Tumors (GIST).
- Whether CT or MRI can improve the pretreatment evaluation of invasive cervical cancer.

Functional Imaging of Low Activity Genes by ICMIC Researchers

For years, cancer researchers have been studying certain highly important, but low activity, genes in their work with animal models. The "activity" of a gene — usually measured by how much protein it is making — helps the scientist understand how the gene is affecting the biology of the cell. However, the protein levels of low activity genes are often too minute to measure. To overcome this difficulty, one team of *In Vivo* Cellular and Molecular Imaging Center (ICMIC) researchers, studying the gene for prostate specific antigen (PSA) in mice, recently developed a technique known as two-step transcriptional amplification (TSTA). In the first step, they changed the mouse's PSA gene so that it would produce a small amount of a special protein whenever the PSA gene was active. For the second step they added a separate gene that will produce large quantities of an easily measured fluorescent chemical, when in the presence of even small amounts of the special protein. Then, by measuring fluorescence, they determined the activity level of the PSA gene. The ICMIC researchers expect to develop the TSTA approach for study of a variety of low activity genes, adding to our understanding of a number of cancers and how to prevent, detect, and treat them.

Nanoscience — New Opportunities for Detection, Monitoring, and Intervention

Recent advances in understanding the molecular basis of cancer raise the possibility of diagnosing, treating, and monitoring cancer with increasingly specific, even individualized therapies. A number of researchers in the field of nanoscience have started to develop synthetic spheres of molecules that can seek out and examine cancer cells. These special spheres, referred to as nanoparticles because they are thousands of times smaller than a single cell, can carry a variety of specially designed molecular-sized attachments that allow them to act as a type of biosensor. These remarkable nanotechnology innovations can be designed to seek out, analyze, and treat cancer cells — all without harming healthy cells. NCI-supported researchers are developing such a biosensor to locate brain tumor cells and tag them for easy imaging. The biosensor can then be targeted with an external laser beam to activate a special chemical attachment designed to kill the cell. Other exciting projects in nanotechnology are taking shape in laboratories across the country. Although human testing is years away, with proper funding and interdisciplinary cooperation, scientists envision making significant progress in this field within 5 to 10 years. Ultimately, we look for a day when many cancer patients will be effectively diagnosed, treated, and monitored with a simple injection and non-invasive monitoring rather than with surgery, chemotherapy, radiation, or other conventional therapies.

The **Digital Mammography Imaging Screening Trial**, another large-scale ACRIN trial, is comparing the diagnostic power of digital mammography to conventional, film-based mammography. Over 6,000 women have enrolled at 18 locations across the United States, and another 10 sites will be added in 2002. ACRIN is also helping to design and conduct the NCI-funded **National Lung Screening Trial** (NLST), which will determine the merit of spiral computed tomography (CT) for lung cancer detection compared to X-ray screening. NLST will utilize the infrastructure developed in the up-and-running **Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial** to enroll 50,000 current or former smokers for screening at 30 study sites throughout the United States.

Other NCI-sponsored networks are also evaluating the use of imaging technologies. For example, the American College of Surgeons Oncology Group is determining the value of **positron emission tomography**, or PET, for lung cancer staging. In addition to supporting these and other large-scale clinical trials for imaging technologies, NCI is providing infrastructure to support **early phase clinical testing of imaging agents and probes** at various centers and NCI-supported programs around the country.

NCI also recognizes the crucial place of partnerships to translate budding imaging technologies into practices that improve patient care. For example, NCI's **Novel Imaging Technologies program** supports collaboration of academic scientists with industry and foreign institutes to create unique imaging technology. One team of NCI-funded investigators is developing the next generation of the PET/CT scanner for improved localization and evaluation of difficult-to-pinpoint cancers and therapeutic monitoring.

Furthermore, NCI is working to integrate imaging into a broad cross section of cancer clinical trials as a way to make the trials more efficient. For example, NCI cooperative groups are working with the Cancer Therapy Evaluation Program, or CTEP, to identify how to use imaging as a biomarker or surrogate marker — perhaps instead of a biopsy — to demonstrate the effectiveness of a treatment. In April 2002, NCI held a workshop, "Role of Biological Imaging in Radiation Oncology." Scientists identified the next steps needed to integrate functional and molecular imaging with radiation therapy to improve tumor control while minimizing damage to healthy tissues.

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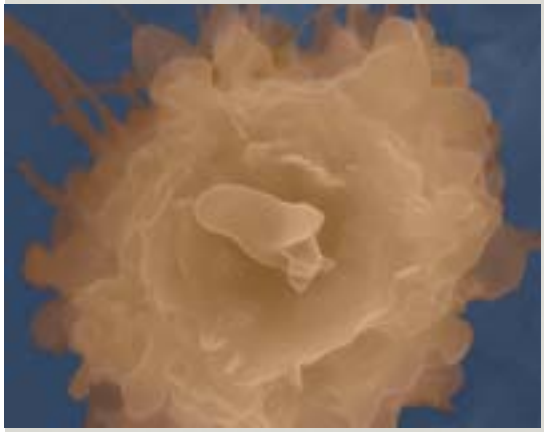
Harnessing Apoptosis to Destroy Cancer Cells

In 1972, John Kerr, Andrew Wyllie, and Alistair Currie published a paper describing a little known and curious form of cell death that today is one of the most intensively studied topics in modern biology. They reported on programmed cell death, which they labeled "apoptosis," noting that it was distinctly different from the long recognized cell death process known as necrosis. In necrosis, a cell ruptures, causing inflammatory cells to rush in to clear away the debris.



A muscle cell undergoing apoptosis.

Apoptosis, however, is clean and quick: a cell shrinks and is rapidly digested by neighboring cells. Although biologists have long known that apoptosis is important in embryogenesis, Kerr, Wyllie, and Currie were the first to observe that it occurs in mature cells. They also were the first to hypothesize that its failure contributes to a variety of diseases, including cancer.

Unfortunately, this groundbreaking paper created little excitement in the scientific community until **more than ten years later** when Nobel prize winner H. Robert Horvitz used the microscopic roundworm, *C. elegans* to explore how a single fertilized egg develops into an adult organism. As he painstakingly followed each of the developing worm's 1,090 cells to their ultimate fate, he was surprised to see that 131 cells died via apoptosis as the worm matured into adulthood. With this observation, he substantiated the prediction made by Kerr and his colleagues that apoptosis occurred beyond embryogenesis. **By 1986,** Horvitz determined that three genes were responsible for regulating apoptosis in *C. elegans* and demonstrated for the first time that this process is genetically programmed. Horvitz and his colleagues also determined that these genes are broadly conserved among plants and animals, indicating that apoptosis has been sustained through evolution and has a universally important biological function. These findings greatly energized apoptosis research. **Over the next 15 years,** scientists confirmed that apoptosis plays a central role in developing organisms by shaping neural and immune systems and molding tissue specificity, and in mature organisms by establishing a natural balance between cell death and renewal as it destroys excess, damaged, or abnormal cells.

Additional studies have revealed that apoptosis occurs through two distinct cellular pathways, one of which is initiated by signals outside the cell, the other by signals from within. Both pathways converge inside the cell, turning on a central executioner family of proteins known as caspases. Caspases act as knives, cutting up proteins inside the cell and digesting the cell from within. Because caspases become activated early in apoptosis and irreversibly launch a cell's death machinery, scientists sought their trigger. **In 1996,** Xiaodong Wang and colleagues discovered that caspases are activated by cytochrome c, a critical protein component of the mitochondria (the energy-producing structures of cells). With this finding, scientists began to study the mitochondria to determine how apoptosis functions in the cell, and malfunctions in disease.

Connecting Failed Apoptosis and Cancer

The link between apoptosis and cancer was not established **until 1988** when David Hockenbery and colleagues characterized the *bcl-2* gene. *Bcl-2* was first discovered in B cells (an immune cell) from patients with follicular lymphoma (an immune system cancer). Hockenbery determined that the normal *bcl-2* is a suicide "brake" gene — it produces a protein that blocks apoptosis. In lymphoma patients, the abnormal form of the gene is overactive, causing the anti-apoptosis protein to be overproduced. Cancer develops as more and more B cells are generated and fail to die. This finding, a milestone in cancer research, revealed that increased cell division was not the only way that tumors could develop. Cells could also

become potent promoters of tumor growth by avoiding programmed cell death.

Throughout the 1990s, scientists gathered considerable information about *bcl-2*. They determined that increased bcl-2 protein production occurs in several cancers (B cell leukemias, lymphomas, colon and prostate cancers, and neuroblastoma) and is linked with poor disease outcome. In addition, overexpression of the *bcl-2* gene may confer resistance to chemotherapeutic drugs. **In 1997,** scientists determined that the bcl-2 protein prevents apoptosis by blocking the release of cytochrome c from inside the mitochondria. Because resistance to the apoptosis-inducing effects of chemotherapy appears to develop from changes within the mitochondria of tumor cells, scientists now are working to develop a complete picture of how bcl-2 controls cytochrome c release so that they can improve the suicide-provoking effects of cancer treatments as well as thwart a cancer cell's ability to evade these drugs.

Although *bcl-2* was the first component of the cell suicide mechanism to be identified, this dauntingly complicated process has many genetic controls. For example, the p53 protein, known as the guardian of the human genome, serves as an important tumor suppressor because it either blocks the cell division of a genetically damaged cell or triggers apoptosis by causing damage to the mitochondria and cytochrome c release. In 55 to 70 percent of human cancers, however, genetic mutations render the p53 protein deficient and cells with DNA damage can continue to accumulate. Loss of p53 function is associated with tumor aggressiveness and resistance to anti-cancer treatments.

Evidence indicates that acquiring apoptosis resistance is a hallmark of most, and perhaps all types of cancer. As scientists learn more about how apoptosis fails in cancer, they also are gaining a greater understanding of why many tumors are resistant to the killing effects of radiation and chemotherapy, which both act by inducing cell suicide. These insights can inform efforts to overcome treatment resistance and offer important clues about targeted new drugs that encourage selective apoptosis. Researchers are exploring how apoptosis is regulated, how it might be repaired through genetic therapies, and how it can be selectively triggered, through tailored treatments, to induce suicide in cancer cells while leaving healthy cells alone.

Triggering Apoptosis with New Cancer Drugs

Clinical trials are **currently underway** to test the efficacy of new apoptosis-inducing drugs. Velcade, a new agent jointly developed by NCI and Millenium Pharmaceuticals, targets the proteosome, a device inside a cell that functions like a cellular "garbage disposal," removing abnormal, aged, or damaged proteins. By blocking proteosome activity, Velcade causes proteins to build up in the cell. One of these proteins is BAX. In the normal cell, the BAX protein promotes apoptosis by blocking bcl-2 activity. As BAX levels increase in response to Velcade, the cell undergoes apoptosis. Velcade may prove to be a versatile cancer treatment because it appears to be equally effective against cancers that do or do not overexpress the *bcl-2* gene and seems to overcome a tumor's ability to develop chemoresistance. In a Phase II clinical trial of patients with progressing multiple myeloma, Velcade stabilized the disease in 77 percent of the trial participants. Based on this encouraging result, researchers are planning a Phase III trial to compare Velcade to dexamethasone, a chemotherapy now used to treat multiple myeloma. Other Phase II trials will determine the drug's effectiveness in treating breast cancer, non-small cell lung cancer, melanoma, sarcoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and neuroendocrine and renal cancers.

Genasense is another apoptosis-inducing agent that is being tested for its clinical use. Developed by the Genta Company, this drug blocks the production of the bcl-2 protein and leaves cancer cells more vulnerable to apoptosis-inducing chemotherapies. NCI and Genta are co-sponsoring clinical trials in lung cancer and leukemia patients to determine whether pretreatment with this drug followed by state-of-the-art chemotherapies improves treatment outcome.

GOAL

Understand and apply the most effective communications approaches to maximize access to and use of cancer information by all who need it.

Cancer Communications

The Opportunity

From primary prevention to survivorship and end of life, only communication can enable people to make informed cancer-related decisions and adopt behaviors to improve their health. Yet, substantial research reveals gaps between the information people want and what they receive. As in other areas of life, people with less income and education are also disadvantaged with respect to health communication. This is especially evident with patient-provider communication.

NCI leads our Nation's cancer communications research and development efforts and funds many of the Nation's most innovative and rigorous health communications researchers. We are also building a substantial storehouse of effective communication strategies that are saving lives through interventions that reduce smoking, boost fruit and vegetable consumption, and increase the numbers of people who are screened for cancer.

But where we are in communicating about cancer is not where we want to be. We must learn more about the science of communication and more rapidly translate successful intervention research into practice. In particular, we must apply what we have learned to improving the health of underserved populations.

Communicating science-based information about cancer poses challenges, opportunities, and responsibilities. In this new communications century, our ability to use multiple methods of communication designed to reach specific audiences and individuals is likely to produce greater impact than any single approach.

We understand that for every person who needs information about cancer, for every patient and family member who receives the diagnosis of cancer, the experience is individual and unique. Our increasingly refined capacity to tailor messages can help translate science into useful information for people through an ever-expanding menu of communication choices. New technologies and tools should extend but not replace one-to-one communication between health-care providers and their patients.

Our greatest challenge is to work with others to find ways to speed the process from discovery to dissemination to assure that caregivers, public health officials, patients, and the public have needed information at the appropriate time, in a form that is comprehensible and useful as well as culturally and linguistically appropriate. This is our challenge, and it is also our responsibility.

Progress In Pursuit of Our Goal

Establishing New Data Collection and Analysis Strategies

The **Health Information National Trends Survey** will be fielded in late 2002 to collect nationally representative data every two years from 8,000 randomly selected adults about the public's need for, access to, and use of cancer-related information. NCI staff are developing protocols to assure that the scientific community has rapid access to the data and that some reports are created especially for lay persons. In future surveys, we plan to also collect data on cancer survivors' use of different media, their risk perceptions, cancer-related behaviors, personal cancer experiences, and perceived communications needs.

Amid the controversy on the efficacy of mammography as a life saving measure this past year, NCI quickly mounted an **omnibus survey on women's reactions to the mammography controversy**. Survey results showed that women with lower

levels of education and income were more likely to be confused and less likely to have good sources of information about mammography. Most participants indicated that they plan to continue to get mammograms in spite of the conflicting evidence. Respondents who said they had enough information to make a decision were more than three times as likely to plan on getting screened than women who said they did not have enough information. These findings will inform our future communications planning in this area. We are also planning an international research effort.

Accelerating the Pace of Research and Development of Interventions

NCI-funded researchers are assessing the **changing information needs of cancer patients undergoing chemotherapy and radiation therapy**. Study results will help NCI assess the communication concerns, problems, patterns, and needs of newly diagnosed patients during active treatment and the early recovery period.

NCI convened the Consumer-Provider Communication Research Symposium in January 2002 to bring together eminent scholars from a broad range of disciplines to identify **major gaps in the research literature on patient-doctor communications**. Gaps identified include the need to better understand the roles played by caregivers other than doctors and the nature of their interactions with patients, the changing relationship between patient and doctor, the use of diverse settings and channels, and the need for improved research methodologies.

NCI is funding interdisciplinary **Centers of Excellence in Cancer Communications Research** to focus on the advancement of cancer communication science using new and/or improved syntheses, theories, methods, and interventions. We are also developing and marketing collaborative interdisciplinary **training and career development opportunities** for health communication researchers and practitioners.

Increasing Access To and Use of Cancer Information

Four **Digital Divide Pilot Projects** were conducted in collaboration with NCI's Cancer Information Service (CIS) to identify effective new strategies for providing underserved populations with access to relevant online cancer information.[1] Overall computer use also increased, including the amount of health information sought via the Internet three months after training.

NCI has launched an **improved Web site and search engine** that combines the information formerly available on NCI's CancerNet and cancerTrials sites in user-friendly topical formats. The first four months following launch saw use increase more than 30 percent.[2]

NCI revised ***Clear Horizons*** and the ***Guia para dejar de fumar*** (Guide to Quitting Smoking) as part of a smoking cessation project targeted to Medicare beneficiaries in collaboration with the Centers for Medicare and Medicaid Services. Approximately 10,000 copies of *Clear Horizons* and 400 copies of the *Guia* have been distributed.

5 A Day for Better Health is one of the most widely recognized health promotion messages in the world. The program is the largest public-private partnership for nutrition in the United States. The Department of Health and Human Services, including NCI and the Centers for Disease Control and Prevention, and the U.S. Department of Agriculture recently signed an agreement to formalize and expand their commitment to promote the *5 A Day* message nationwide, and particularly, in American schools.

After a successful pilot, the regional Cancer Information Service (CIS) now offers **LiveHelp**, which uses instant messaging technology to provide real-time responses to cancer inquiries on NCI's Web site, averaging 1,000 user sessions per month. CIS plans to pilot LiveHelp again as part of NCI's **smokefree.gov** Web site, scheduled for launch in 2002. In March 2002, one CIS regional office began piloting the use of e-mail to respond to inquiries received through the Web.

As part of a joint NCI and Agency for Healthcare Research and Quality initiative, researchers were funded to develop and evaluate a **primer to help people use numbers in health**. Three basic risk communication tools will supplement the primer: cancer risk charts, prevention benefit charts, and standard disease summary templates.

[1] Results at **dccps.cancer.gov/eocc/ddpp-awards.html**

[2] Go to **cancer.gov** to use this enhanced set of online resources.

Cancer Communications

G O A L

Increase knowledge about, tools for, access to, and use of cancer communications by the public, patients, survivors, and health professionals — with a special focus on diverse populations — to accelerate reductions in the U. S. cancer burden.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Establish new data collection and analysis strategies to support cancer communications planning and evaluation. **$ 4.00 M**

- Analyze data from the Health Information National Trends Survey (HINTS), the first national communications survey of U.S. populations and make results rapidly available to researchers and program planners. $1.00 M
- Conduct an Internet-based version of HINTS to determine feasibility of online data collection in order to increase response rates and minimize costs. $0.50 M
- Conduct a HINTS survey of cancer survivors in parallel with the HINTS public survey to collect data on survivors' use of different media, their risk perceptions, cancer-related behaviors, and personal cancer communications experiences. $0.50 M
- Conduct regular surveys to assess and analyze the public's reactions to media communications on cancer for use in program planning and evaluation. $1.00 M
- Map the information terrain to understand the nature of the information that is being provided to different audiences through different media, including the Internet. $0.50 M
- Assess women's communication needs related to mammography screening worldwide. $0.50 M

2. Accelerate the pace of research and development of cancer communication interventions. **$ 18.50 M**

- Continue to support the Centers of Excellence in Cancer Communications Research (Ongoing commitment of $10.00 M per year beginning in Fiscal Year 2003).
- Strengthen interdisciplinary research training in strategic areas, including risk communications and interactive health communications. $1.50 M
- Support basic communications research to accelerate discoveries about how cancer information is processed and used. $2.50 M
- Support innovative applied communication studies, testing how integrated electronic and interpersonal communication systems can improve health. $5.00 M
- Create a New Media Collaborative (NewMediaCo) to answer important questions about tailored communications and the new media. $4.00 M

- Establish FAST (Facilitate and Accelerate Science and Technology) Track Funding for researchers who are conducting health communications research using state-of-the-art communications and informatics technologies. $3.00 M
- Conduct research to understand and enhance communication between doctors and patients. $2.50 M

3. Develop a communications menu to increase access to and use of cancer communications by all populations, especially underserved populations. **$ 5.75 M**

- Work with collaborators to fund additional pilot projects to increase Internet access and use and evaluate outcomes. $1.00 M
- Develop new tools and products to facilitate cancer communications for the public, patients and their caregivers, underserved populations, advocacy groups, health professionals, and cancer communicators. $1.00 M
- Develop a strategic plan and program for low-literacy populations. $1.00 M
- Develop and promote a media toolkit to facilitate the media's use of NCI's resources in preparing cancer-related stories. $0.50 M
- Continue to build and nurture the *5 A Day for Better Health* program partnerships and campaigns to reach underserved populations. $1.00 M
- Develop and promote, to grantees and organizations, toolkits for planning communications programs, with a special focus on underserved populations. $0.50 M
- Develop cancer information for Hispanics/Latinos. $0.75 M

4. Improve the science of dissemination and the dissemination of science to assure that all our citizens realize the benefits of research investments. **$ 7.50 M**

- Provide supplemental funding support for investigators to diffuse and disseminate NCI-funded evidence-based interventions. $4.00 M
- Expand, update, and disseminate the searchable databases of cancer-related communication research reports accessible to researchers and program planners. $0.50 M
- Conduct research and development on innovative strategies for dissemination. $3.00 M

Management and Support **$ 4.00 M**

Total **$39.75 M**

New Cancer Communications Efforts Further Accelerate Discovery to Delivery

Effective communication is critical all along the corridors, from discovery in the laboratory to development of new drugs and other interventions to delivery of those interventions in the clinic. With adequate funding in Fiscal Year 2004, we can continue and expand current efforts while implementing new initiatives.

- New public surveys to assess reactions to media coverage about cancer will aid us in communication planning and evaluation, especially in evaluating the public's reaction to controversial coverage.
- New training workshops and toolkits about cancer science for journalists will enhance the quality and quantity of media coverage about cancer.
- NCI's International Breast Cancer Screening Network, a voluntary consortium of 25 countries, will develop best practices for their international population-based screening mammography programs and standardize and summarize existing information and decision tools for all member countries.
- We will partner with the National Science Foundation or the National Institute of Mental Health to conduct basic communications research to accelerate discoveries about how cancer information is processed and used.
- Applied communications studies will test how integrated electronic and interpersonal communication systems can improve decision making, facilitate positive changes in health behavior, and improve health.
- A New Media Collaborative will develop theory driven definitions of the active ingredients in tailored communications, agree on common measures, identify a minimum set of essential core mechanisms, and conduct process-to-outcome analyses.
- The FAST (Facilitate and Accelerate Science and Technology) Track Funding program will be employed to overcome current system barriers that result in long delays in moving ideas to innovative technologies and funding.

NCI has developed an education program entitled the ***Facing Forward*** **Series** to equip patients, families, and healthcare providers with information about what to expect following cancer treatment. Publications on cancer survivorship issues for health professionals and family care are planned for 2003.

NCI researchers are studying **how to communicate more effectively with low literacy populations**. Lessons learned will be synthesized with an understanding of the needs of low literacy populations to develop an actionable strategic plan and program. NCI currently offers low literacy materials on the topics of pain and clinical trials.

Improving the Science of Dissemination and the Dissemination of Science

NCI has collaborated with the American Cancer Society (ACS) to adapt two successful NCI-funded intervention studies to create ***Body & Soul: A Celebration of Healthy Living***, a nutrition program to be delivered through African-American churches. The program is an example of effective research dissemination to communities, as well as successful research collaboration between NCI and ACS.

NCI funded the dissemination of two promising intervention programs and products: ***Sunny Days, Healthy Ways***, Grade 6-8 Sun Safety Curriculum, and ***5 A Day for Better Health*** dissemination. In the first project, researchers will compare the efficacy of disseminating Sunny Days to public elementary schools and licensed childcare facilities in several areas and test whether dissemination is improved by providing Web-based training and technical support.

Launched in January 2002, **NewMediacy** now has more than 300 subscribers. The listserv has summaries of and links to the latest communications related data and reports. Important findings include data on doctor-patient communications and on the public's use of online health information.

NCI, in partnership with the Center for the Advancement of Health, the Robert Wood Johnson Foundation, and the NIH Office of Behavioral and Social Sciences Research, is sponsoring a **conference on what we know, what we need to know, and what we need to do** to accelerate the adoption of evidence-based cancer prevention and control interventions.

Progress against cancer takes place not only in the laboratory and the physician's office but in an environment of heightened public health concern. Prevention bolsters our defense against cancer. The delivery of quality care is paramount when cancer strikes an individual. A network of support is critical to our increasing number of survivors, their families, and a population that is aging. — *Andrew C. von Eschenbach, M.D.*

Addressing Areas of Public Health Emphasis

This past year, as NCI has once again examined its priority research areas, four stand out as having special significance not only for increasing our understanding of cancer but for informing aggressive policy decisions and planning for public health programs. We can no longer ignore, for example, the pervasiveness of media support for tobacco use in this country. Television and films continue to glamorize smoking and its purported benefits for stress relief, and smoking is still touted to our young far too often as a rite of passage to adulthood or as a gateway to approval.

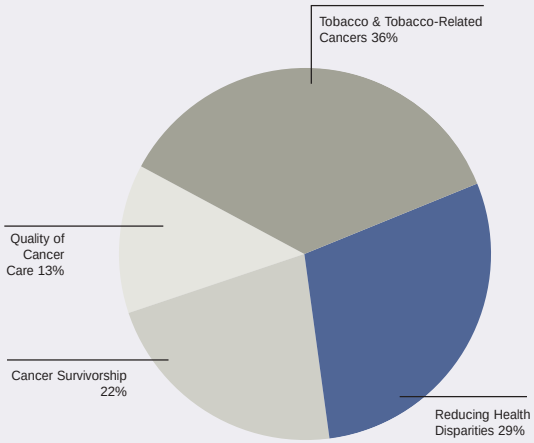
In our 2004 budget proposal, we give special attention to four areas of public health emphasis. They are NCI Challenge areas for *Improving the Quality of Cancer Care* and *Reducing Cancer-Related Health Disparities* and Extraordinary Opportunity areas in *Cancer Survivorship: Improving Treatment Outcomes and Quality of Life* and *Research on Tobacco and Tobacco-Related Cancers*.

We must act on behalf of the millions of people in our country today who do not receive appropriate care for their cancer, do not get the kind of support they need to deal with the emotional, physical, and psychological effects of treatment and survivorship, or are among the untold numbers who are denied proper care because of social position, economic status, cultural or language barriers, or geographic location. In each instance, we need better science to understand the complexities in these areas. As we study disparities, we can take action against them where the causes are clear. And there is a pressing need to address the challenges posed to our Nation's healthcare system by the rising incidence of cancer as a result of the aging U.S. population. For all Americans, we need evidence-based interventions that will prevent cancer from occurring and improve the health and quality of life for those who are affected by cancer.

FY 2004 Increase Request for Areas of Public Health Emphasis

(dollars in thousands)

Quality of Cancer Care	$ 27,000
Reducing Health Disparities	$ 61,350
Cancer Survivorship	$ 46,000
Tobacco & Tobacco-Related Cancers	$ 76,000
Total	**$210,350**



GOAL

Improve the quality of cancer care by strengthening the scientific basis for public and private decision making on care delivery, coverage, purchasing, regulation, and standards setting.

Improving the Quality of Cancer Care

The Challenge

The nine million Americans living today who have had cancer, including the 1.3 million who will be diagnosed in 2002 and the 500,000 who are in the last year of life, all hope that they receive the best medical treatment and care possible. Unfortunately, far too many will not receive this caliber of care. The Institute of Medicine's National Cancer Policy Board (NCPB) recently reported that the "ad hoc and fragmented cancer care system" in the United States "does not ensure access to care, lacks coordination, and is inefficient in its use of resources." Testimonies of cancer patients, families, and providers, summarized in the President's Cancer Panel Report, *Voices of a Broken System: Real People, Real Problems*, point to a number of barriers to high quality cancer care. These include system and financial limitations, the inadequacy of patient information and provider education, poor management of cancer-related symptoms, and lack of timely referral to palliative and hospice care.[1]

Drawing from the NCPB report, we define quality cancer care as the provision of evidence based, patient centered services throughout the continuum of care in a timely and technically competent manner, with good communication, shared decision making, and cultural sensitivity, with the aim of improving clinical outcomes, including patient survival and health related quality of life. Substantial disagreement exists about what constitutes optimal care, especially from the patient's perspective. Therefore, it is critical that we advance understanding of how to measure, monitor, and improve the quality of cancer care. We must:

- Define core outcome measures and standardize core process measures to identify those interventions that have been shown to improve cancer care.
- Build a stronger data and methods "infrastructure" for conducting quality of care analyses, including studies at both the individual and population levels.
- Incorporate symptom management and palliative care across the cancer continuum, through cancer quality improvement research and translation efforts.
- Ensure that effective therapies demonstrated in clinical trials are incorporated into community practice.
- Enhance cancer communications for patients, their families, and caregivers.
- Strengthen collaborative relationships with Federal agencies and private organizations to ensure that the best available scientific evidence guides cancer care decisions.

Progress Toward Meeting the Challenge

Developing Core Measurements

In 2001, NCI convened the **Cancer Outcomes Measurement Working Group**, composed of 35 internationally recognized experts in measurement, oncology, and the social sciences, to assess alternative approaches for improving patient centered *outcome measures* such as quality of life, economic burden, and satisfaction with care. A major barrier to comparing findings is the lack of standardization in measuring outcomes, like health related quality of life. In response, working group members recommend that outcome measures be selected from the small set that has been adequately validated. In addition, NCI should support research to improve our ability to compare study findings, conduct sound meta-analyses, and adopt user friendly, computer adaptive survey administration.

Standards for *process measures* of quality cancer care are being developed through a major new NCI

[1] Institute of Medicine, National Research Council, *Ensuring Quality Cancer Care*, 1999.
President's Cancer Panel, *Report of the Chairman 2000-2001, Voices of a Broken System: Real People, Real Problems*, September 2001.

Prostate Cancer Outcomes Study Sheds Light on Treatment Choices

The Prostate Cancer Outcomes Study (PCOS), the most comprehensive survey ever undertaken on prostate cancer outcomes, was initiated in 1994 to evaluate variations in practice and the impact of therapies on health related quality of life. Study findings are helping men, their families, and clinicians make more informed choices about treatment alternatives. They include:

- Reports showing that, while physicians order bone scans on approximately two-thirds of all new prostate cancer patients and computed tomography (CT) exams on about one-third of new patients, less than five percent of the imaging studies done for newly diagnosed prostate cancer patients show evidence of metastases. In contrast, for men with serum PSA levels greater than 50 ng/ml and Gleason scores ranging from 8-10, the imaging studies were positive in over 60 percent of the cases.
- Evidence that men with clinically localized prostate cancer who are treated with a radical prostatectomy are more likely to experience urinary and sexual dysfunction than those treated with external beam radiation therapy. Bowel dysfunction, on the other hand, is more common among men receiving external radiation therapy.
- Evidence that men aged 75 or older more often received conservative treatment, such as hormonal therapy alone or watchful waiting, than aggressive treatment such as radical prostatectomy or radiation therapy.
- A finding that for men younger than 60, use of aggressive treatment was similar among white, African-American, and Hispanic men. Among men 60 years old and older, African American men underwent aggressive treatment less often than did white men or Hispanic men.

NCI plans to follow the 3,500 PCOS participants for 10 years after diagnosis to ascertain and verify deaths, maintain contact with respondents, and conduct a survey ten years out to assess long-term changes in disease-related quality of life.[2]

[2] appliedresearch.cancer.gov/PCOS/index

collaboration with other Federal agencies and the private sector. This **Cancer Care Quality Measurement Project** (CanQual), conducted under the auspices of the non-profit National Quality Forum, is identifying core process measures for treatment, survivorship, and end-of-life care for the major tumor sites, as well as measures that apply to all tumor sites, such as palliative care.

Strengthening the Science Base

NCI established the **Cancer Care Outcomes Research and Surveillance Consortium** (CanCORS) in 2001, launching a single study of treatment patterns and quality of care over time in large cohorts of newly identified cancer patients. CanCORS investigators are combining data from registries, medical records, insurance claims, and patient and provider surveys to assess the care received by a sample of 5,000 colorectal and 5,000 lung cancer patients across the United States. This research will investigate the impact of selected interventions on patient centered outcomes, dissemination of state-of-the-art therapies in the community, modifiable risk factors, and disparities in cancer care and outcomes by racial/ethnic group and socioeconomic status. Recognizing the potential value of large cohort studies, the American Society of Clinical Oncology (ASCO) is conducting a similar study, focusing on breast and colorectal cancer, as part of its National Initiative on Cancer Care Quality. NCI and ASCO have signed a Memorandum of Understanding that stresses sharing information and progress on these complementary efforts. The forerunner to CanCORS is the landmark **Prostate Cancer Outcomes Study**, the first longitudinal study of quality of life for men living with prostate cancer. (See sidebar on this page.)

NCI's recently established **Patterns of Care/Quality of Care Program** (POC/QOC) is drawing from the Surveillance, Epidemiology, and End Results (SEER) registry data to investigate adoption of recommended treatments for the most common cancers. POC/QOC studies provide the most authoritative data on trends in treatment patterns for breast, colorectal, and ovarian cancer and results will be disseminated through professional education activities in collaboration with professional societies. The **Cancer Research Network**, a consortium of researchers affiliated with 10 major not-for-profit HMOs, has provided the mechanism for NCI to obtain better data more quickly on patterns of cancer care from multiple perspectives. The work of the **Breast Cancer Surveillance**

Improving the Quality of Cancer Care

G O A L

Improve the quality of cancer care by strengthening the scientific basis for public and private decision making on care delivery, coverage, purchasing, regulation, and standards setting.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Develop core process and outcome measures for assessing the quality of cancer care. **$ 5.50 M**

- Support research to improve patient-centered outcomes measurement, including development of tools to enhance data collection and statistical studies to facilitate the "cross-walking" of scores among competing instruments. $2.00 M
- Continue to provide supplemental funding for the Cancer Care Quality Measurement Project to identify additional core process measures. $1.00 M
- Support research to evaluate and enhance dissemination and use of core process measures and develop new measures where needed. $2.50 M

2. Strengthen the methodological and empirical foundations of quality of cancer care assessment. **$15.00 M**

- Sustain support at $7.5 million per year for Cancer Care Outcomes Research and Surveillance Consortium studies.
- Sustain support for Cancer Research Network population laboratories at $5.0 million per year for cancer control research, with additional emphasis on the quality of cancer care in community settings.
- Support Pattern of Care/Quality of Care (POC/QOC) studies on levels, trends, variations, and dissemination of effective treatments and collaborate with other Federal agencies and professional societies for education on quality of care improvement. Provide support for new Rapid Response Special Studies (RRSS) to facilitate methodological and pilot investigations. Integrate results from these studies with Cancer Intervention Surveillance Modeling Network models to predict the effects of treatment dissemination on trends in survival and mortality. $3.00 M
- Increase support for analyses of the Surveillance, Epidemiology, and End Results and Medicare (SEER-Medicare) database to investigate the use and outcomes of selected cancer interventions. $2.00 M
- Based on results of completed and ongoing POC/QOC, SEER-Medicare, and RRSS studies, support intervention studies and demonstration programs for improving referral patterns and treatment where sub-optimal performance has been documented. $2.00 M
- Based on ongoing feasibility studies, link tumor registry information to Medicaid and private payer administrative data to investigate whether interventions are reaching and improving the health of individuals aged 65 or younger. Assist private insurers in creating and analyzing claims linked to tumor registry data by leading a workshop based on the experience of SEER-Medicare and SEER-Medicaid investigators. $2.00 M
- Continue to support innovative research on economic and delivery system determinants of the quality of and return on investment for new clinical approaches to prevention, screening, and treatment services. $2.50 M

- Sponsor new studies to strengthen the methodological foundations of outcomes research and quality of care assessment, including studies on the integration of evidence based performance measures at provider and health system levels. $2.00 M
- Support the establishment of physician networks and databases for tracking and monitoring cancer screening practices. $1.50 M

3. Incorporate symptom management and palliative care into the full spectrum of cancer quality improvement research and translation efforts, from initial treatment, through survivorship, and at the end of life. **$ 1.00 M**

- Integrate existing and newly developed knowledge about effective symptom management and palliative care.
- Incorporate evidence based palliative care practices more fully into NCI's education and information products and spotlight Internet accessible information.
- Educate health professionals on ways to better integrate and deliver symptom management and palliative care, using best-practice standards.

4. Enhance quality of care research within, and beyond, the NCI clinical trials program. **$ 1.50 M**

- Sponsor meetings to bring together leading researchers and stakeholders to assess the state of the art, identify key research questions, and develop a strategy for assessment of patient outcomes for clinical trials. Disseminate resulting information. $0.50 M
- Using knowledge gleaned from a workshop on the diffusion of medical innovations, support studies examining the rates and patterns of adoption of important therapies across the entire spectrum of delivery systems. $1.00 M

5. Improve the quality of cancer care by strengthening cancer communications. (See Cancer Communications plan, pages 72-76.)

6. Ensure that the best available scientific evidence about quality measures and assessment informs Federal decision making. Share new knowledge and collaborate to identify, develop, and monitor progress on core measures of cancer care quality. **$ 3.00 M**

- Continue to support interagency demonstration projects organized through the Quality of Cancer Care Committee (QCCC), a forum for coordinating Federal activities. $2.00 M
- Capitalize on the collective clinical and policy expertise of the QCCC to provide technical assistance and advice to public agencies and private organizations upon request.
- Foster collaboration among QCCC members (particularly the Centers for Disease Control and Prevention, the Centers for Medicare and Medicare Services, and the Agency for Healthcare Research and Quality), the states, and private organizations to support ongoing development of a national cancer data system for monitoring trends in cancer care and identifying population disparities. $1.00 M

Management and Support **$ 1.00 M**

Total **$27.00 M**

NCI Collaborates with Federal Partners To Ensure That the Best Available Evidence Informs Decision Making

Through the Quality of Cancer Care Committee, NCI currently supports three interagency projects:

- The Health Resources and Services Administration and Centers for Disease Control and Prevention collaborative to build on a chronic care model to develop "breakthrough changes" to improve screening, referral, and follow-up for breast, cervical, and colorectal cancer for underserved populations.
- The Centers for Medicare and Medicaid Services collaborative to increase awareness and improve delivery of the Medicare colorectal cancer screening benefit among Medicare beneficiaries and their physicians.
- The Department of Veterans Affairs (VA) collaborative to improve use of evidence about good practice for ongoing improvements in screening, surveillance, treatment, and end-of-life care for colorectal cancer in the VA healthcare system.[3]

[3] hsrd.research.va.gov/queri/CRC_web_announcement.doc

Consortium investigates factors associated with high quality screening mammography in community practice, including hormone replacement therapy and breast density, family history, age, and examination technique.

Studies linking SEER and Medicare data continue to provide insight into quality of care issues including:

- Nearly equivalent costs of breast conserving surgery versus mastectomy for early-stage breast cancer.
- Potential disparities by race, ethnicity, or age in the receipt of chemotherapy for colon and ovarian cancer.
- Significantly reduced rates of postoperative and late urinary complications for men undergoing prostatectomy, when performed in a high-volume hospital by a surgeon who performs a high number of such procedures.

Improving Symptom Management and Palliative Care across the Cancer Continuum

The *Improving Palliative Care for Cancer* report[4] from the Institute of Medicine's National Cancer Policy Board identified gaps in symptom management and palliative care research. Information on how to better measure, evaluate, and improve symptom management is now emerging from a variety of initiatives:

- Research supported by NCI through the Cancer Outcomes Measurement Working Group, CanQual, CanCORS, and Quality of Cancer Care Committee projects
- The 2002 NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue
- Clinical trials on supportive and palliative care topics such as cachexia, pain, and symptom reduction as well as new research concepts that examine depression in cancer patients through the NCI Community Clinical Oncology Program
- NCI- and NIH-supported studies on complementary and alternative medicine at the end of life

Enhancing Quality of Care Research within the NCI Clinical Trials Program

The NCI National Clinical Trials Program provides an ideal venue to assess quality of care through the incorporation of valid and reliable health related quality of life endpoints into clinical study design. A workshop on the diffusion of medical innovations will be held in 2003, setting the stage for studies to examine why some highly promising therapies successfully move into clinical practice while others do not.

Strengthening Cancer Communications

Ultimately, improved cancer care depends on our ability to communicate messages about prevention, treatment, patient care, survivorship, and end-of-life issues to the research community, care providers, patients, and payers. See pages 72-76 for information on NCI cancer communication efforts.

Ensuring That the Best Available Science Informs Decision Making

NCI established the Quality of Cancer Care Committee (QCCC) in 2000 to improve the quality of Federal-level decision making about cancer care. Its membership includes the Federal agencies involved in cancer care delivery, coverage, regulation, standards setting, or conducting research on the quality of cancer care. (See sidebar at the top of this page.)

[4] Institute of Medicine, National Research Council, *Improving Palliative Care for Cancer*, 2001.

Sustained Investment in Studying Cancer Trends Improves Knowledge and Understanding of Cancer

This is a report on progress toward objectives outlined in previous years as part of the NCI Challenge for Studying Emerging Trends in Cancer. While we are not requesting additional funding increases in this area, the following efforts will continue to produce the information and resources needed for high quality, well informed research, program planning, and health policy.

The **Surveillance, Epidemiology, and End Results** (SEER) Program serves as the foundation for a national system of data resources on all aspects of cancer surveillance. We have:

- Increased coverage and made it more representative of the entire population, including racial/ethnic minorities and groups living in rural areas — through expansion and partnerships with the Centers for Disease Control and Prevention and state cancer registries.
- Expanded quality data on risk factors; health behaviors; extent of disease, treatment, and lifestyle; and quality of life for cancer survivors — through public and private partnerships.
- Provided scientists with information (generated by Economic Studies in Cancer Prevention, Screening, and Care and Cancer Surveillance Using Health Claims-Based Data Systems) to assess trends, quality, and the cost of cancer care.
- Conducted Patterns of Care studies to assess the quality of care that cancer patients receive.[1]

We have **new research methods** in place to monitor cancer interventions, ensure the accuracy of questionnaires for self reporting, track nutritional health objectives, and estimate the economic cost of cancer. For example:

- The Cancer Intervention and Surveillance Modeling Network uses computer-based modeling to study the need for and the effectiveness of cancer interventions.
- The recently completed study, Observing Protein and Energy Nutrition, is improving our ability to use and interpret dietary assessment data.[2]
- The Family History of Cancer Assessment Study is assessing the accuracy of reports of cancer family histories.

NCI is also co-funding, with the National Science Foundation, projects in data visualization, software for geospatial analysis, and graphical display of data.

Our **data system and methodological resources** are being distributed widely and integrated into a number of public and private sector efforts. For example:

- The *Atlas of Cancer Mortality* shows geographic patterns of cancer death rates and a companion Geographic Information Systems provides tools for using the Atlas.
- The Cancer Profiles system identifies areas in greatest need of cancer control activities.
- The Tobacco Use Supplement to the Current Population Survey tracks progress in tobacco control.
- The Diet History Questionnaire is used for epidemiologic and surveillance studies.
- The National Health Interview Survey Cancer Control Topical Module is used to evaluate national progress in achieving cancer objectives.

The annual *Cancer Progress Report*, first released in 2001, informs the public, policy makers, advocates, and health professionals of progress in the Nation's fight against cancer.[3] The *Annual Report to the Nation on the Status of Cancer*, published in collaboration with several partners, provides an update on cancer rates and trends in the United States.[4]

For more detail about these and other similar initiatives, go to **appliedresearch.cancer.gov** and **surveillance.cancer.gov.**

[1] See page 79 for more information.
[2] See page 52 for more information.
[3] **progressreport.cancer.gov**
[4] **seer.cancer.gov/reportcard**

GOAL

Understand the fundamental causes of health disparities in cancer, develop effective interventions to reduce these disparities, and facilitate their implementation.

Reducing Cancer-Related Health Disparities

The Challenge

The unequal burden of cancer in our society is more than a scientific and medical challenge. It is a moral and ethical dilemma for our Nation. Certain populations experience significant disparities in cancer incidence, the care they receive, and the outcomes of their disease. These differences have been recognized, or at least suspected, for some time. Now, they are being documented with increasing frequency and clarity.

Our challenge today is to:

- Fully understand the fundamental causes of cancer health disparities, including the influence of social position, economic status, cultural beliefs and practices, environmental exposures, genetics, and individual behavior.
- Develop effective interventions to address these disparities.
- Actively facilitate their implementation.

If there are ways we fund or perform cancer research that favor one person or group over another, we must discover and mend those ways. If there are ways we distribute the benefits of our research that contribute to the very real social and economic disparities in who develops cancer, who survives cancer, and the quality of that survival, we must improve our distribution. And if we can influence policy to improve care, we must exercise that influence.

Recognizing that disparities must be overcome if we are to significantly reduce the Nation's cancer burden, NCI established a dedicated center to direct and coordinate an Institute-wide plan to address key disparity issues. The scope of planning will incorporate all research areas within NCI's organizational structure — basic biology, epidemiology, genetics, prevention, communication, cancer control, diagnostics and treatment development, and survivorship.

Healthcare policymakers, providers, payers, and other stakeholders must be empowered to provide equal access to proven interventions for cancer prevention and control for all populations. NCI must collect and synthesize the scientific evidence and provide leadership to help ensure that policies and services bring the benefits of research to all Americans.

Progress Toward Meeting the Challenge

NCI is working to identify cancer health disparities and their underlying causes. For example, NCI, together with national, state, and local partners, is investigating the **causes of disparities in cervical cancer mortality**. While mortality for this disease has fallen three-fold nationwide in the past 50 years, some geographic areas experience persistently high cervical mortality rates. Researchers, clinicians, patient advocates and others will meet to review surveillance and background data for high mortality areas and articulate the key issues and recommendations for action. This information will be disseminated to Federal, state, and local policy makers.

NCI has funded a landmark, five-year **Southern Community Cohort Study** that will enroll and follow 105,000 people — two thirds of whom will be African Americans — in six southeastern states to determine why African Americans are more likely to develop and die from cancer. Genetic, environmental, and lifestyle factors that contribute to cancer development will be identified, and important health information about low income and rural populations of all races is also anticipated.

NCI has launched an investigation into the impact of the "racialization" of scientific inquiry and disparate patient outcomes. We are also working to establish interdisciplinary research **Centers for Population Health and Health Disparities** to better understand the interaction of social, cultural, and physical

environmental determinants of cancer incidence and outcomes and the behavioral and biologic factors that contribute to them. This trans-NIH initiative is also supported by the National Institute of Environmental Sciences, the National Institute on Aging, and the Office of Behavioral and Social Science Research and seeks to develop more effective interventions.

The **California Health Interview Survey**, sampling more than 55,000 respondents, is expanding understanding of the interplay of race, ethnicity, socioeconomic factors, and other social and cultural influences on cancer risk factors such as tobacco use, diet, and screening. With several partners, NCI has implemented programs to address the cancer health disparities that are being identified. For example, NCI sponsors 18 **Special Populations Networks for Cancer Awareness Research and Training** that build relationships with community-based programs, foster cancer awareness activities, increase minority enrollment in clinical trials, pilot projects that will lead to the development of grant applications for new and innovative research, and develop junior biomedical researchers from minority and underserved communities. Collaborations with NCI Divisions and clinical/academic partnerships among Network awardees and Cancer Centers, academic institutions, and Clinical Cooperative Groups are essential to all of these activities.

NCI is partnering with the Health Resources and Services Administration, the Centers for Disease Control and Prevention, and the Institute for Healthcare Improvement in a **Health Disparities Collaborative** to improve delivery for underserved populations throughout the United States. The Collaborative focuses on colorectal, breast, and cervical cancer screening and clinical follow-up for people who traditionally lack access to quality healthcare.

In 2003, the radiation oncology-based **Cancer Disparities Research Partnerships Program** will expand radiation oncology clinical trials in three geographically dispersed institutions serving large numbers of Native Americans, African Americans, Hispanics and rural Appalachians. The program is also expanding dissemination and diffusion channels using novel telemedicine and teleconferencing to connect participating institutions, their academic partners, and NCI clinical facilities and experts.

NCI continues to provide **health disparities training for new scientists** through the Cancer Prevention Fellowship Program. Interest in health disparities continues to grow, with 6 of 15 entering fellows in 2002 expressing strong interest compared with none in 1999. In 2003, the Cancer Disparities Research Partnerships Program will support minority clinical investigators, nurses, data managers, and others at institutions new to cancer disparities research.

Results of Recent Research on Cancer-Related Health Disparities [1]

Social Circumstances May Contribute to Lower Survival Among African Americans with Advanced Non-Small Cell Lung Cancer (NSCLC). Researchers assessed more than 500 patients receiving systemic chemotherapy for advanced NSCLC, between 1989-1998, and found that African Americans in the study were more likely to present with a poor performance status and greater weight loss. African Americans in the study were also more likely to be unmarried, disabled, unemployed, or Medicaid recipients, suggesting that social circumstances may be the cause of poorer prognostic profiles in African Americans.

Educational Interventions Increase Cervical Cancer Screening Among Chinese Americans. NCI-supported investigators in Seattle found that direct mailing of culturally and linguistically appropriate educational materials and home visits by outreach workers can increase participation in cervical cancer screening in the Chinese-American population.

African American Men Are at Greater Risk for Advanced Prostate Cancer. Res
ethnic differences among men who develop advanced prostate cancer and found that African American men were at greater risk of advanced disease than Hispanic men and had about twice the risk of non-Hispanic Whites. After adjusting for clinical and sociodemographic variables, such as higher socioeconomic status, the difference for African Americans persisted but disappeared for Hispanics. Additional research on biologic markers, genetic susceptibility, and socioeconomic factors is needed to better explain disparities and determine how this information can help reduce cancer risk for these populations.

[1] See also Highlights of Progress, pages 8-13.

Reducing Cancer-Related Health Disparities

GOAL

Understand the fundamental causes of health disparities in cancer, develop effective interventions to reduce these disparities, and facilitate their implementation.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Expand research on the causes of health disparities in cancer. $16.20 M

- Identify gaps in research for cancer health disparities by reviewing Federal and voluntary organization research portfolios. Use findings to update NCI's strategic plan, guide research and partnership efforts, and set priorities for new cancer health disparities research support. $5.20 M
- Expand the knowledge base through fundamental cancer control research, including:
  - – International collaborative studies on social determinants of cancer and cancer-related disparities through supplements to NCI-supported Centers for Population Health and Health Disparities. $2.00 M
  - – Expanded epidemiologic studies exploring racial/ethnic cancer disparities. $3.00 M
  - – Investigations of physician, patient, and health system factors influencing cancer care quality among racial/ethnic minorities and other underserved populations. $3.00 M
  - – Research on biologic pathways through which behavioral, social, physical, and environmental factors influence cancer-related health disparities, including genetic polymorphisms, psychoneuroimmunologic factors, and differential responses to therapy. $3.00 M

2. Develop effective interventions to reduce cancer health disparities. $ 9.50 M

- Increase collaborative research among the Special Populations Networks for Cancer Awareness Research and Training, NCI, and other Federally funded research networks. $3.00 M
- Assess the efficacy and cost effectiveness of patient navigator programs in populations experiencing serious cancer-related health disparities. $1.00 M
- Collaborate with service delivery components of the Federal government to support new intervention research for women who have not been screened or who are substantially under screened for breast and cervical cancer, emphasizing sociocultural determinants in planning, implementing, and evaluating these interventions. $3.50 M
- Address disparities in risk, access to prevention interventions, quality cancer care, and clinical trials through formal affiliations and supplemental funding to NCI Cancer Centers using existing links with and direct funding to Minority-Serving Institutions. $2.00 M

3. Expand our ability to define and monitor cancer-related health disparities. $ 6.00 M

- Enrich understanding of cancer health disparities through new population-based state and regional surveys that provide information on socioeconomic and cultural factors. $1.00 M
- Conduct methodologic research to ensure cross-cultural equivalence in survey, epidemiological, and clinical research involving cancer risk factors. $1.00 M
- Collect risk factor and screening data for small populations defined by geographic, racial/ethnic, socioeconomic, and other characteristics. $4.00 M

4. Facilitate the implementation of new policy, community and clinical interventions, and evaluate their impact on health disparities. **$ 17.90 M**

- Support a series of meetings with representative stakeholders to review evidence, develop collaborations, and create action plans for interventions to reduce or eliminate cancer health disparities. $0.50 M
- Increase minority and underserved population access to state-of-the-art prevention and treatment clinical trials:
  - Expand clinical trials outreach to under-represented populations and increase participation in trials at established minority-based oncology sites. $3.00 M
  - Provide supplements to fund a nurse case manager and a patient navigator at each of approximately 15 Cancer Centers, 20 Cooperative Group sites, and 10 Community Clinical Oncology Program sites that have demonstrated a commitment to expand minority participation in clinical trials. $4.40 M
- Expand dissemination and promotion of research results and evidence based interventions to reduce cancer health disparities.
  - Expand local and regional partnerships to overcome health disparities among medically underserved populations. Disseminate models for success to communities with similar infrastructure barriers. $2.50 M
  - Expand support for research-practice partnerships between Federally funded cancer control investigators and state and local health program practitioners to increase community based cancer prevention and control research and evidence based interventions in underserved communities. $2.00 M
  - Establish a Dissemination/Diffusion Research Grants Program to (1) study social, environmental, and behavioral barriers to adopting evidence-based cancer prevention and control interventions by public health officials and community clinicians, (2) test new hypotheses for reaching underserved populations in under-resourced community health settings, and (3) develop, apply, and evaluate dissemination and diffusion interventions to reduce cancer health disparities. $4.00 M
  - Expand NCI's integrated low literacy program by customizing cancer information materials for targeted audiences. $1.50 M

5. Expand minority investigator competition for and minority population involvement in health disparities research. **$ 9.75 M**

- Recruit 3 additional minority scientists and physicians to the Cancer Prevention Fellowship Program to focus on health disparities research. $0.75 M
- Expand the Continuing Umbrella of Research Experiences Program to encourage high school to graduate level minority students to enter careers in health disparities research. $2.00 M
- Increase minority participation in clinical trials through an NCI fellowship training program for healthcare providers and other forums. $1.00 M
- Expand support for the Science Enrichment Program to attract minority high school students to careers in science and medicine. $1.00 M
- Fund 20 new cancer education grants for healthcare provider continuing education, outreach programs in underserved communities, and accrual of minority and underserved populations to NCI-supported treatment and prevention trials. $5.00 M

Management and Support **$ 2.00 M**

Total **$61.35 M**

G O A L

Reduce the adverse effects of cancer diagnosis and treatment and optimize outcomes for cancer survivors and their families.

Cancer Survivorship: Improving Treatment Outcomes and Quality of Life

The Opportunity

Entering the new millennium armed with new insights into biology, including information from the sequencing of the human genome, we are beginning to see the fruits of the "War on Cancer" launched in 1971. Once almost uniformly fatal, cancer has become for many, a chronic illness, and for growing numbers, a curable disease. There are an estimated 8.9 million cancer survivors in the United States today. An impressive 14 percent of these individuals were originally diagnosed over 20 years ago.

Cancer survival has risen steadily over the past three decades for all cancers combined. In the absence of other competing causes of death, current figures indicate that for adults diagnosed today, 60 percent can expect to be alive five years later. As past and future advances in cancer detection, treatment, and care diffuse into clinical practice, the number of survivors can be expected to increase. Fewer deaths from cardiovascular disease and the aging of the population will contribute to this trend.

While cancer survivors are living longer, we have limited knowledge and many questions about the health status, functioning, and quality of life for most of those who are post-treatment: What are the most common late effects of treatment? Who is at risk and can they be protected? Can treatment-related injury to normal tissue be prevented or reversed? What proportion of survivors will experience recurrent or second malignancies? Who should be following these survivors to detect disease recurrence? What constitutes "optimal surveillance" and what is the cost of such follow-up care? Do medical, psychosocial, or behavioral interventions reduce morbidity in these populations?

What is clear is that most of our current treatments, although benefiting the patient overall, will produce some measure of adversity. In some cases, these effects can have a profound impact on survivors' health and quality of life. For example:

- A quarter of deaths among childhood cancer survivors are due to late consequences of treatment — e.g., second malignancies, cardiac failure. In one large study, 46 percent did not believe that their treatment could have put them at later risk for a serious health problem. This knowledge gap has implications for optimal care.
- Breast and lymphoma patients exposed to systemic chemotherapy are at increased risk for problems with cognitive functioning and some may be genetically more susceptible to this chronic effect of treatment.
- Between a quarter and a third of patients undergoing bone marrow or stem cell transplant suffer from symptoms of post-traumatic stress disorder (PTSD). Similar numbers of parents (especially mothers) of children treated for cancer also experience PTSD symptoms, even years after their children are treated.
- Female brain cancer survivors are eight times more likely to experience separation or divorce than male survivors.

The adverse effects of cancer treatment remain poorly documented and understood. As presently configured, our surveillance databases (e.g., from NCI's Surveillance, Epidemiology, and End Results Program and other tumor registries) often cannot identify a patient's current health status and phase of survivorship — whether in active treatment, disease free, or dying of cancer. More research is needed to address issues of survivorship for specific cancers as well as for populations that have been under-represented in previous research, such as the elderly.

Cancer survivors and their family members face unique and uncharted consequences of illness and treatment. Information about survivors is critical if we are to:

- Help patients make decisions now about treatment options that will affect their future.
- Tailor therapies to maximize cure while minimizing adverse treatment related effects.
- Develop and disseminate evidence based interventions that reduce cancer morbidity as well as mortality and facilitate adaptation among cancer survivors.
- Improve quality of care, control costs, and equip the next generation of physicians, nurses, and other healthcare professionals to provide not just the science but also the art of comprehensive cancer medicine.

Recent Institute of Medicine reports have identified the need for the following survivorship research that will lead to increased length and quality of life for those diagnosed with cancer.[1]

Monitoring Adverse Long-Term or Late Effects of Cancer and Its Treatment

As children and adults with a history of cancer are living longer and data from NCI research studies are maturing, the nature and extent of long-term and late effects are being documented and reported: neurocognitive problems, premature menopause, gastrointestinal system dysfunction, cardiorespiratory system dysfunction, sexual impairment, infertility, chronic fatigue and pain syndromes, second malignancies, and others. Identification of patients at increased risk for complications of treatment and information on interventions to reduce those risks will help patients, their families, and their providers negotiate critical decisions. With NCI's recent expansion of the Surveillance, Epidemiology and End Results and National Clinical Trials Programs, our ability to track and monitor disease and care-related outcomes among survivors through these types of surveillance mechanisms is developing.

Understanding the Role of Behavioral and Socio-Cultural Factors in Patient Outcomes

There is growing appreciation of the role that sociocultural and behavioral factors play in patient outcomes. Research shows that many survivors and their families experience significant psychosocial outcomes: fear of recurrence, sense of isolation, anxiety and depression, employment and insurance discrimination, altered body image, and relationship difficulties. While we know that human behavior can have a profound impact on how cancer is managed and may also affect disease-free or overall survival, we are not currently using this information in the systematic delivery of care. Nor do we understand cancer's consequences for millions of family members affected by this illness, many of whom may themselves be at increased risk for cancer due to shared cancer causing genes, lifestyle, and/or toxic exposures. As cancer care increasingly is pushed into the outpatient setting, the economic, physical, and emotional burden on family members is increasing. We have, to date, failed to fully appreciate this additional at-risk population or taken advantage of the opportunity to provide these vital caregivers with supportive or health-promoting interventions as part of standard cancer care.

Understanding Genetic Risk and Treatment

It is expected that with the decoding of the human genome, our ability to identify hereditary cancer risk patterns and genes associated with susceptibility to treatment-related late effects will accelerate. Using tissue and blood samples from survivors to track outcomes holds the promise of helping us to better understand how cancer-causing genes operate and what therapies may be effective in controlling their effects. It will also permit us to understand which therapies work best and for whom they are successful. An increasing number of cohort studies[2] are focusing on cancer survivors.

Training Researchers and Disseminating Research Findings

It is critical to disseminate the resulting research findings across disciplines so that clinicians and researchers and other experts from the biomedical and social sciences can use the new knowledge for further research, intervention development, trend analysis, and advocacy.

[1] *Ensuring Quality Cancer Care*, 1999. **nationalacademies.org/publications**
Improving Palliative Care for Cancer, 2001. **nap.edu**.
Improving Palliative Care for Cancer, Summary and Recommendations, 2001. **nap.edu**.

[2] In a cohort study, the same patient group is studied over a period of time.

Cancer Survivorship: Improving Treatment Outcomes and Quality of Life

G O A L

Reduce the adverse effects of cancer diagnosis and treatment and optimize outcomes for cancer survivors and their families.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Expand research efforts to understand the biological, physical, psychological, and social mechanisms, and their interactions, that affect a cancer patient's response to disease, treatment, and recovery. — **$9.50 M**

- Fund cohort and case control studies that examine the prevalence and incidence of late effects, in particular among survivors five or more years post-diagnosis. $3.00 M
- Fund behavioral and epidemiological studies that examine both negative and positive physiologic and psychosocial effects, and their correlates, of cancer on survivors who are post-treatment. $5.00 M
- Identify the genetic and/or phenotypic markers of susceptibility to treatment-related adverse effects and gene-environment interactions, using molecular epidemiological research. (See page 50, Objective 1.)
- Support efforts to synthesize the research, and its implications for future directions, with respect to the role of sociocultural, behavioral, emotional, and spiritual factors in survivor and family outcomes and their willingness to adopt appropriate surveillance and health maintenance behaviors post-treatment. $1.50 M
- Ensure that efforts to expand our knowledge base, with respect to the impact of cancer and its treatment on survivor's outcomes, includes attention to diverse cancer sites and under-represented groups — e.g., certain ethnic groups, persons diagnosed at 65 or older, older survivors with competing health problems, rural populations, low-income groups, or those with limited education.

2. Accelerate the pace of intervention research in order to reduce cancer-related chronic and late morbidity and mortality. — **$12.00 M**

- Expand research on the most promising and cost effective medical, behavioral, educational, and psychosocial interventions to address cancer patient needs for improved quality of life — e.g., reducing cancer-related symptoms such as distress, pain, and nausea; minimizing post-treatment organ dysfunction; promoting healthy practices such as exercise, smoking cessation, diet change; and addressing individual needs. This research would include examination of the impact on the patient of type, intensity, and length of well characterized and controlled interventions on appropriate intermediate biomarkers — e.g., immune functioning, cortisol levels, PSA levels. $9.00 M
- Support the development of interventions that involve family members and friends versus those directed only at the cancer survivors, as well as interventions that target minority and medically underserved populations. $3.00 M

3. Develop tools to assess the quality of life and care of post-treatment cancer survivors and their family members. — **$ 5.50 M**

- Promote the development of new instruments to assess health-related quality of life beyond the active treatment period and evaluate the validity of existing instruments.

This should include efforts to accelerate the pace of development of common toxicity criteria for late effects of cancer treatment. $2.00 M

- Promote the development and testing of screening tools that identify individuals who are at high risk for poor physical, psychosocial, or behavioral outcomes and assess the impact of such screening on patterns and outcomes of care. $2.00 M
- Use applied and theoretical statistics to: establish the criteria or cutoff scores needed to qualify a change in function as clinically significant — e.g., improvement, impairment — and examine the value placed on aspects of quality of health by survivors across the continuum of care. $0.50 M
- In collaboration with other NIH institutes (e.g., the National Institute on Aging or the National Heart, Lung, and Blood Institute), develop measures that permit the evaluation of co-morbidities that are both cancer and non-cancer related. $1.00 M

4. Enhance NCI's capacity to track outcomes for cancer survivors. $ 5.50 M

- Pilot the expansion of data collection on health-related outcomes for survivors in selected Surveillance, Epidemiology and End Results registries. $1.00 M
- Develop and support the infrastructure for clinical trials groups to follow patients long-term (up to 5-10 years post-treatment). $2.00 M
- Establish a separate registry for pediatric cancer survivors seen within the pediatric clinical trials network. $2.50 M

5. Ensure the development and dissemination of new interventions and best practices, in collaboration with other Federal and health- or cancer-related professional and non-profit organizations. $ 3.50 M

- Promote the development and dissemination of best practice guidelines for follow-up care, surveillance, and monitoring of cancer survivors who have completed initial cancer treatment. $1.25 M
- Support studies to test the adoption and impact of best practices in post-treatment care of survivors. $1.50 M
- Develop and disseminate curricula and standards for the delivery of effective psychosocial and supportive care across the illness continuum. $0.75 M

6. Expand the scientific base for understanding the biologic and physiologic mechanisms in the adverse late effects of current and new cancer treatments. $ 9.00 M

- Fund pre-clinical studies in clinically relevant tissue and animal models to examine the incidence of and mechanisms for certain physiologic late effects of cancer treatment (e.g., fatigue, organ dysfunction, second malignancies) and test novel strategies to modulate treatment-related toxicities. $3.00 M
- Support research that seeks to: investigate the neuropsychologic impact of cancer therapy — e.g., mechanisms underlying post-chemotherapy cognitive dysfunction; examine chemotherapy induced organ dysfunction — e.g., mechanisms underlying cardiac sequelae of doxorubicin treatment; explore the mechanisms of delayed radiation induced organ fibrosis and dysfunction; and explore long-term immunologic effects of cancer and cancer treatment. $6.00 M

Management and Support $ 1.00 M

Total $46.00 M

Highlights of Recent Cancer Survivorship Related Research [3]

Tool Enhances Studies on the Long-Term Consequences of Cancer Treatment. Among the critical issues for cancer survivors are the "late effects" of their illness and treatment that sometimes do not show up for a number of years. To better define these consequences, the NCI is funding a program to update the common toxicity scoring system to incorporate the LENT score, Late Effects of Normal Tissues. This scoring system enables investigators to:

- Compare newer treatments with the current regimens for treating all cancers.
- Relate laboratory research to the severity of effects experienced by patients when investigating molecular mechanisms for late tissue damage.
- Facilitate the development, for use in clinical trials, of interventions to prevent, reduce, or possbly reverse "late effects" of cancer treatment.

Adjusting Chemotherapy Dosage Reduces Incidence of Congestive Heart Failure among Cancer Survivors. Treatment with the chemotherapy drug anthracycline, or more specifically its metabolic byproduct doxorubicin, places survivors at risk for congestive heart failure following their cancer treatment. At greatest risk are women, African Americans, and younger patients. NCI-supported researchers have discovered that moderately reducing the overall cumulative dosage of anthracycline can reduce the incidence of congestive heart failure from seven to well under one percent.

Growth Hormone Replacement Helps Children Safely Achieve Normal Height following Treatment for Leukemia. Seventy to eighty percent of children with Acute Lymphoblastic Leukemia are cured with current treatments. However, because of treatment-related effects, many of these survivors are short in stature as adults. Some of these patients have been treated with growth hormone therapy over the years, although the medical community has not been in agreement about the effectiveness or the safety of such treatment. An NCI-sponsored team of investigators recently found that replacing growth hormones, in those survivors where it is low, effectively induces "catch-up growth" and most patients reach normal, or near normal, adult heights. This study also examined safety issues, confirming that this treatment does not cause relapse or second cancers. Although further study is warranted, these results suggest that growth hormone therapy is a safe treatment choice that will benefit many adult survivors of this disease.

Lung Cancer Survivors Retain Quality of Life. Although lung cancer is one of the most common cancers in the United States, little is known about the quality of life of lung cancer survivors. NCI-supported scientists recently analyzed self-reported indicators from five-year survivors of non-small cell lung cancer for factors that have the most effect on quality of life, such as other diseases, pulmonary function, depression and anxiety, tobacco use, social and spiritual well-being, and demographics. Notably, half of the survivors said their cancer had made a positive change in their life and the majority were "very hopeful." Risk factors for poorer quality of life are strongly linked to depression, suggesting potential interventions by health care providers. The number of comorbid conditions (other diseases) experienced by the survivors was a weak indicator of overall life quality, although those with higher income and with few comorbid conditions reported better physical well being. Nonwhite participants rated greater than whites for overall quality of life as well as for mental health. This study, for the first time, highlights the range of experiences for long-term survivors of this disease and provides insights for potential rehabilitation. The complex interactions of quality of life by race/ethnicity and socioeconomic status deserve further study.

Social Interventions Can Benefit Breast Cancer Survivors. An NCI-sponsored study of breast cancer survivors over a four-year follow-up period shows that health-related quality of life is influenced by the survivor's availability of social networks. On average, socially isolated women were more adversely affected by breast cancer, scoring lower on "role function," "vitality," and "physical function," compared to the most socially integrated women. The level of a patient's social integration is an important factor and appears to explain more of this variance than differences in treatment or tumor type. The study results suggest that rehabilitation programs should incorporate interventions that address the availability of adequate social support among breast cancer survivors.

[3] See also Highlights of Progress, pages 12-13.

I had leukemia as a kid. The treatment was rough, but my family and friends and all of the doctors and nurses really helped me keep a positive frame of mind — even when the cancer came back a few years later and I had to go through treatment all over again. I know I'm fortunate to be alive.

Adult Survivors of Childhood Cancers

An estimated 8.9 million Americans with a history of cancer other than non-melanoma skin cancer or in situ diseases were alive in 1997. Of these, an estimated 270,000 were survivors of childhood cancers. Survival rates from childhood cancers have increased dramatically over the past few decades, due in large part to the fact that nearly 80 percent of children with cancer are treated in clinical trials by multi-specialty medical teams.

For an increasing number of patients of all ages, cancer is a chronic disease, not a fatal one. Over many years of survival, patients may find their cancer journey marked by a series of successes and failures that may include the management of recurrences, physical and cognitive side effects, or even second cancers. As treatments and supportive care have improved, however, it has become possible to reduce recurrences and minimize or eliminate some of the delayed or long-term side effects commonly experienced by patients treated with less advanced therapies.

As I've gotten older, I've needed to keep that positive attitude. I've had some side effects from my treatment — I'm diabetic and my heart and lung functions are reduced somewhat. But I take my medicine, and pay attention to my diet, my stress level, and things like that. I think that taking good care of myself will help keep me cancer free and help me have the fullest possible life.

We recognize more and more that surviving cancer involves factors related to the way our bodies and minds respond to the changes brought on by the disease. We need to better understand these changes and how they influence cancer progression, treatment, and life after treatment. For example, evidence is emerging that psychosocial factors that influence immune or endocrine processes may influence the development or progression of certain cancers.

NCI supports research on the relationship of particular treatments to specific short- and long-term side effects. We also need to understand, for example, the biological basis of these side effects, why some patients are able to be more optimistic than others about treatment success (even in the face of a difficult prognosis), and what contributes to people's ability to overcome side effects that impact their mobility, physical comfort, or psychological well being.

I still check in from time to time with the doctors who treated me, but since I became an adult, most of my health care is provided by my primary care physician.

Because the large and growing number of long-term survivors is a relatively recent phenomenon, no clearly defined system exists for monitoring and managing long-term and delayed side effects or second cancers. Research is needed to determine the most appropriate roles of oncology specialists, primary care providers, and survivors themselves in their lifelong follow-up care.

G O A L

Understand the causes of tobacco use, addiction, and tobacco-related cancers and apply this knowledge to their prevention and treatment.

Research on Tobacco and Tobacco-Related Cancers

The Opportunity

Lung cancer, the leading cause of cancer death, would be a rare disease in the absence of smoking. Smoking is the leading cause of cancers of the lung, mouth, larynx, esophagus, and bladder, and plays a role in cancers of the pancreas, cervix, and kidney. The devastating impact of tobacco use and tobacco smoke exposure on the incidence of cancer, heart and lung disease, stroke, and other serious illnesses is both compelling and conclusive. Tobacco use causes more premature deaths (approximately 430,000 per year in the United States) than do all drugs of abuse combined. In 2002, about 170,000 people will die of cancer because of their use of tobacco products. A major challenge in the fight against tobacco-related cancers is that addiction to nicotine drives the continued use of tobacco even when the user is fully aware of increased risk of disease and premature death. Some people will continue to smoke even as they undergo treatment for a life threatening disease.

NCI's commitment to preventing, diagnosing, and treating tobacco-related cancers began more than 40 years ago. To remain at the leading edge of this important area of research, NCI must devote additional resources to address the complex challenges of tobacco use. Research recommendations related to tobacco use made by NCI's Lung Cancer Progress Review Group echo many of the Institute's priorities, such as:

- Developing and expanding new approaches to the biology and treatment of nicotine addiction.
- Conducting basic biological research on the effects of tobacco exposures including the differential toxicity of various tobacco products.
- Continuing and evaluating current and planned population-based tobacco control efforts.
- Detecting and treating tobacco-related cancers and metastatic disease.

NCI also has a special concern for the health of former smokers who, despite quitting, now comprise about half of those diagnosed with lung cancer. The development and marketing of new tobacco products also is of great concern. Scientists must examine the toxicity of these products as well as evaluate whether or not "harm reduction" is a viable public health strategy. NCI's commitment to research on tobacco and tobacco-related cancers is reflected in our investments both in basic biological research on the effects of tobacco exposures and in community-based studies of smoking prevention and cessation programs.

Progress in Pursuit of Our Goal

Defining Biological, Behavioral, and Social Bases of Tobacco Use and Addiction

NCI is advancing tobacco research to answer questions related to why people begin to use tobacco, become addicted, and have difficulty stopping use of tobacco products, as well as genetic and environmental factors that influence tobacco use and addiction.

Funding for **Transdisciplinary Tobacco Use Research Centers** (TTURCs), located within seven academic institutions, is approaching its fourth year of sponsorship by NCI, the National Institute on Drug Abuse (NIDA), and the Robert Wood Johnson Foundation. These centers are supporting a broad array of studies, including projects evaluating new models of nicotine addiction, the role of genetic and environmental factors in smoking initiation and persistence, methods for preventing tobacco use across cultures, and determinants of relapse. TTURC sponsored research continues to inform us.

- Certain genes regulating the activity of the neurotransmitter dopamine help determine which smokers are able to quit. Although these genes do not appear to influence the effectiveness of

the medication bupropion, another gene involved in drug metabolism did predict therapeutic response to treatment.

- Older adolescence, peer smoking, cigarette availability, depression, delinquency, and alcohol use are factors that influence smoking progression in youth. Investigators also found that prenatal exposure to nicotine increases the likelihood that a smoker will progress to regular use. This information is being used to develop cessation programs for high-risk adolescents.
- There are links between specific personality traits and early initiation of smoking. Teenagers with a combination of aggressive and depressive characteristics are at an elevated risk for cigarette smoking. Moreover, depressed adolescents who are highly receptive to tobacco advertising are also at higher risk. These findings lead researchers to believe that tailoring prevention and intervention efforts to encompass these factors could lead to a reduction in youth smoking.

NCI supports 50 research projects related to the **prevention and cessation of tobacco use by children and youth**. Studies reveal that adolescent smokers can experience withdrawal symptoms within one month of smoking initiation. A recently published study showed that not all tobacco dependence in youth is physiological, but that psychological determinants of dependence are equally significant. The authors of this study offered a theory whereby loss of autonomy signals onset of dependence. Loss of autonomy occurs when either the physical or psychological effects of nicotine present a barrier to quitting. Their work resulted in the "Hooked on Nicotine Checklist," a self-administered questionnaire that helps smokers identify ten warning signs of nicotine addiction. This measure offers a validated, theoretically based tool that measures tobacco dependence.

Results from a recent **study of prevalence and predictors of tobacco use among Asian Americans** highlights the need for culturally tailored prevention, cessation, and treatment interventions. Investigators collected data on 1174 Chinese, Korean, Vietnamese, and Cambodian respondents in the Delaware Valley Region of the United States and found that 40.2 percent of respondents had a history of tobacco use and 29.6 percent were current users. Men were more likely than women to smoke, and there were significant differences among never smokers, current smokers, and ex-smokers by sex, ethnicity, educational attainment, and marital status.

Preventing and Treating Tobacco Use and Tobacco-Related Cancers

Research supported through TTURCs, the State and Community Tobacco Control Intervention initiative, and several of the youth and tobacco research projects is producing important new insights and knowledge about the social, biobehavioral, and genetic factors that influence tobacco use and addiction in youth and adults. To complement these efforts, NCI and NIDA initiated a **Working Group on Medication Development for Nicotine Addiction** that explores ways to draw upon NIDA's expertise in addiction research as well as NCI's experience in drug development.

In 2002, NCI opened the doors to the **Tobacco**

International Activities

The World Health Organization (WHO) estimates that four million people die each year worldwide from tobacco-related illness, and if current trends continue, this figure will rise to about 10 million per year by 2030, with 70 percent of those deaths occurring in the developing world.

Examples of NCI support of global tobacco research include:

- Jointly sponsoring the Symposium on Tobacco-Related Cancers with the Japan Society for the Promotion of Science, in February 2002, to bring together international researchers to address molecular, epidemiology, behavioral, cancer control, and clinical aspects of these cancers.
- Co-hosting the Third International Conference on Smokeless Tobacco, in September 2002, with the Centers for Disease Control and Prevention and the Sweden Centre for Tobacco Prevention.
- Providing $1.7 million over the next several years to extend and enhance the research interests of U.S. and collaborating foreign scientists and institutions to combat the growing incidence of tobacco-related illness in the developing world, through the International Tobacco and Health Research and Capacity Building program, led by the NIH Fogarty International Center.
- Initiating a multi-institutional, population-based, case-control study of lung cancer and smoking in Milan, Italy. This study of 4,500 subjects investigates the genetics of nicotine addiction and lung cancer.

Research On Tobacco and Tobacco-Related Cancers

GOAL

Understand the causes of tobacco use, addiction, and tobacco-related cancers and apply this knowledge to their prevention and treatment.

Objectives, Milestones, and Funding Increases Required for Fiscal Year 2004

1. Expand the infrastructure needed to conduct a vigorous research and public health effort consistent with the enormous burden of tobacco-related disease. **$25.50 M**

- Initiate prospective observational studies of the quitting and relapse processes, including the effectiveness of medications. $4.00 M
- Continue support for including tobacco use in the Current Population Survey and increasing the number of non-English language translations. $2.50 M
- Along with other government and non-government institutions, support the use of national, state, and regional tobacco surveillance data and the development of analytical tools, resources, and a network to track and evaluate progress in cancer control. $2.00 M
- Expand the Cancer Intervention and Surveillance Modeling Network (CISNET) to develop models of tobacco use, dependence, relapse, and disease development. $2.00 M
- Renew and expand support for the Transdisciplinary Tobacco Use Research Centers program, in collaboration with relevant public and private organizations. $15.00 M
- Adopt and apply integrated study design models such as BEGIN (Behavior, Exposure, Genetics, Intermediate biomarkers, and Neoplastic markers) to support an interdisciplinary integrated approach to tobacco-related research.

2. Support innovative, integrated investigations to understand and treat tobacco use and addiction. **$19.00 M**

- Capitalize on the breadth of expertise across NIH Institutes by supporting collaborative projects at NCI's new tobacco use research clinic. $1.00 M
- Accelerate the identification of new treatments for nicotine addiction through the implementation of a drug development and clinical trials collaborative group by NCI and other NIH institutes. $4.00 M
- Support research on smoking cessation and relapse prevention in cancer patients and survivors. $2.00 M

Intervention Research Clinic, a state-of-the-science center for tobacco use research by NCI scientists and collaborators, including those in the NCI and other NIH intramural programs. The clinic will be a resource for NIH scientists conducting a range of genetic, epidemiological, basic science, and behavioral research studies and could provide research-based tobacco cessation services to patients from the NIH community.

Translating Research Into Improved Outcomes is an initiative that offers funding opportunities to current NCI-funded investigators to support critical dissemination of promising interventions in the field of tobacco use and other cancer control areas. NCI is also actively involved in a public-private collaborative effort to develop a National Blueprint for Disseminating and Implementing Evidenced-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation.

- Support the identification, development, and dissemination of effective tobacco use, prevention, and cessation interventions to underserved populations. $3.00 M
- Provide supplements to further our understanding of disparities in patterns of tobacco use, cessation, and relapse. $3.00 M
- Collaborate with the Centers for Disease Control and Prevention and other relevant public and private organizations to develop integrated and coordinated communication efforts focused on tobacco use and cessation, including Internet strategies. $1.00 M
- Support innovative, population-based studies involving a whole genome approach to elucidate the genetics of smoking, in collaboration with other NIH institutes and centers. $5.00 M

3. Apply cutting-edge research to better understand and treat tobacco-related cancers. **$ 31.00 M**

- Support clinical and population studies that include tissue and biospecimen resources to investigate the genetic, biological, and behavioral factors influencing vulnerability to smoking dependence and tobacco-related cancer. $6.00 M
- Support studies of the mechanisms of susceptibility to tobacco-related cancers to understand the nature and implications of tobacco products intended to reduce harm. $10.00 M
- Provide supplements to address disparities in clinical care of tobacco-related cancers. $3.00 M
- Support interdisciplinary studies to accelerate development of new, molecularly based lung cancer treatments. $10.00 M
- Enhance the Cancer Information Service's smoking cessation services and research infrastructure to improve treatment of tobacco use. $2.00 M

Management and Support **$ 0.50 M**

Total **$76.00 M**

NCI is funding **preclinical and clinical studies to identify newer, more potent agents that may prevent cancers in former smokers**. The preclinical studies focus on validating surrogate biomarkers[1] for tobacco-related cancers in animal models under experimental protocols that mimic the high-risk smoker. These studies will identify and prioritize agents that prevent cancers in tobacco-susceptible organ systems. The clinical research initiative is supporting four clinical trials evaluating the efficacy of chemopreventive agents in specified cohorts of former smokers. A variety of novel biomarkers as well as imaging modalities, such as the spiral computed tomography (CT) scan, are being examined with regard to their potential utility in chemopreventive studies.

NCI is also supporting the **National Lung Cancer Screening Study** to assess the feasibility of spiral CT to detect early lung cancers.[2]

[1] A surrogate biomarker is a measurable molecular feature (for example, a blood protein) that can be used to monitor the course of a disease or the effects of treatment in place of more long-term outcome measures, such as time to tumor progression, remission, or death.

[2] See page 69.

Public and Private Partnerships and Collaborations

In support of tobacco research collaborative efforts, NCI is:

- Supporting seven Transdisciplinary Tobacco Use Research Centers in partnership with the National Institute on Drug Abuse (NIDA) and the Robert Wood Johnson (RWJ) Foundation to integrate tobacco-related research on genetic susceptibility, sociocultural factors, innovative treatments, and healthcare policy.
- Facilitating an NCI/NIDA Working Group on Medication Development for Nicotine Addiction to develop targeted new treatments.
- Partnering with 10 other public and private organizations to develop a "National Blueprint for Disseminating and Implementing Evidence-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation."
- Organizing and sponsoring a Women, Tobacco, and Cancer Conference with the NIH Office of Research on Women's Health, the DHHS Office of Women's Health, the American Cancer Society, the American Legacy Foundation, and others.
- Sponsoring a National Tobacco Monitoring Research and Evaluation Workshop, in November 2002, along with the Centers for Disease Control and Prevention, RWJ Foundation, and American Legacy Foundation, to improve the utility of tobacco use surveillance systems.
- Participating in NOTURF (National Organization for Tobacco Use Research Funders), a consortium of research funding organizations in the United States and Canada dedicated to fostering communication and action around tobacco research.

Understanding the Interplay Among Tobacco, Other Exposures, and Cancer

NCI is pursuing research opportunities to better understand the interplay among tobacco and other exposures such as alcohol and radon, and a person's cancer risk. This work involves resource intensive, longitudinal, screening, and cohort studies that may involve genetic and biomarker components from tissue, blood, urine, sputum, and other body fluids.

Several studies within the **Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trials** are specifically focusing on tobacco exposure and cancer. These studies are examining the relationship between tobacco and colon adenomas, a comparison of patients with emphysema, and a control group (persons without cancer or related symptoms) to identify genetic factors that may influence susceptibility to this condition. Another investigation will target current and former smokers to identify candidate genes thought to influence smoking.

The **Cohort Consortium**,[3] a group of investigators involved in separate prospective studies of large population groups, will expand their investigation beyond looking at breast and prostate cancer to identifying and studying tobacco-related cancers. These researchers will investigate a rare subtype of lung adenocarcinoma; lung cancer in young people, non-smokers, and families; and rarer tobacco-related tumors such as pancreas and nasal sinuses. Efforts are underway to collect tissue from a broader group of PLCO participants to allow high throughput analysis of new markers of patients with specific cancers.

Additional relevant studies are yielding information on **cancer risk related to the interplay among tobacco and other exposures**. In a case-control interview study on patients with esophageal cancer, researchers found a three-fold excess risk for the disease among those in the highest quartile of body mass index, a predisposition of obese individuals to gastroesophageal reflux disease, and an association between esophageal cancer and cigarette smoking, with little reduction in risk until 30 years after smoking cessation. A large case-control study of bladder cancer is ongoing in the New England region of the United States and Spain to identify occupational bladder carcinogens and to evaluate cigarette smoking (black vs. blond tobacco in Spain) as well as phenacetin-containing analgesics, dietary factors, urination frequency, and pH. Genetic susceptibility markers will be evaluated in relation to bladder cancer risk as well as their interaction with environmental, occupational, and tobacco risk factors.

[3] See page 49.

Index of Selected Topics*

* See also Table of Contents on page 2 for major topics covered in this document.

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- **Professional and Advocacy Organizations:** Alliance for Prostate Cancer Prevention, American Association for Cancer Research, American Public Health Association, American Society for Clinical Oncology, American Society for Therapeutic Radiology and Oncology, The Children's Cause, Lymphoma Research Foundation, National Coalition for Cancer Survivorship, North American Brain Tumor Coalition, Oncology Nursing Society, Robert Wood Johnson Foundation, and Susan G. Komen Breast Cancer Foundation

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- **HHS Agencies**: National Institute on Aging and the Centers for Disease Control and Prevention

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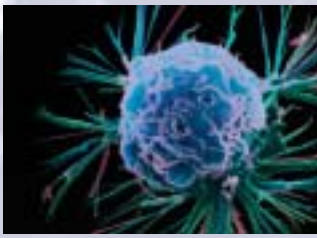
The Nation's Investment in Cancer Research

. . . valuable rewards in cancer signatures research.

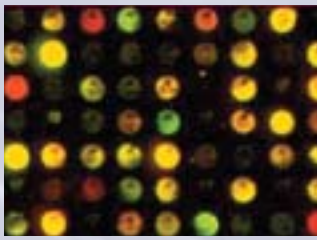
By establishing the "Signatures of Cancer" as a major priority area six years ago, NCI recognized that the cancer field faced an "extraordinary opportunity" that could revolutionize cancer detection and diagnosis. Studies of the molecular underpinnings of cancer revealed that every cell has a molecular signature — a unique biological characteristic that is related to the cell's function in the body. Even more intriguing was the discovery that as a cell transforms from normal to malignant, its signature changes, and this change is a signal of the presence of cancer. We realized that by accurately "reading" the changes that distinguish a cancer cell from its normal counterpart, we could create tools to detect the earliest signature changes of cancer; enhance diagnosis by identifying a tumor according to its molecular features; and advance prevention and treatment by developing interventions that target the molecular features of a tumor. By committing the exceptional resources and developing the innovative new research programs needed to enable creative and high quality signatures research, we are able, today, to demonstrate how our Nation's investment in cancer research is rendering dramatic changes in cancer prevention and care.

Through several ambitious initiatives, investigators are making striking progress in:

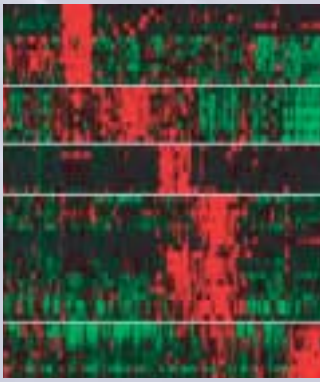
Defining the Signatures of Cancer Cells. Since 1997, Cancer Genome Anatomy Project (CGAP) scientists have worked to uncover all of the molecular information in a cancer cell and its components, including proteins. Today, they have successfully built a nearly complete tumor gene index by identifying over a million genes in more than 40 tissues. Building on this effort, researchers are annotating the types of cells and cancer that express these genes, developing catalogues of chromosomal changes in cancer, and identifying common genetic variations that influence cancer risk in various populations.



Identifying Biomarkers for Early Detection. Launched in 1999, the Early Detection Research Network (EDRN) aims to use the wealth of information coming from CGAP in the development of cancer biomarkers. Through this national research forum, scientists are working to discover, develop, and validate early markers of cancer. EDRN scientists already have successfully discovered a number of biomarkers that allow for the earlier detection of breast, prostate, colon, lung, and other cancers. NCI and EDRN scientists also have effectively applied proteomics to develop a potential screening test that uses patterns of proteins (see picture) to detect ovarian cancer.



Better Distinguishing Different Types of Cancer. The Director's Challenge: Toward a Molecular Classification of Tumors was established in 1999 to support investigators in their efforts to apply gene- and protein-based strategies in the development of new molecular classification schemes for human cancers. This information will improve our ability to accurately classify and diagnose cancer, predict prognosis, and select targeted treatments. Already, these studies are revealing new types and subtypes of cancer that appear to predict which patients will respond to particular therapies. Microarrays (see picture) are helping scientists identify tumor subtypes based on differences in gene expression.



For more information on NCI's cancer signatures research, go to **plan.cancer.gov.**

Valuable World Wide Web Locations

National Cancer Institute **cancer.gov**
National Institutes of Health **www.nih.gov**
Department of Health and Human Services **hhs.gov**
Cancer News **newscenter.cancer.gov**
Cancer Science **newscenter.cancer.gov/sciencebehind**

Cancer Information Service (CIS)

By phone
1-800-4-CANCER (1-800-422-6237)
For deaf and hard of hearing 1-800-332-8615

On the Web
From **cancer.gov,** click on **LiveHelp.**

Other Assistance

Send an email to **cancermail@cips.nci.nih.gov** to request physician services or enter the one-word message "Help" to receive a contents list and ordering instructions for NCI information via email.

Search service for physicians 1-800-345-3300

This Document Online

Access expanded content for this Plan and Budget Proposal, including links to key Websites, at **plan.cancer.gov**. Online links related to the chapters in this book include the following.

National Agendas for Disease-Specific Research
- Progress Review Groups **prg.cancer.gov**
- Research Initiatives **cri.cancer.gov**

Investigator-Initiated Research
- Research Portfolio **researchportfolio.cancer.gov**
- Research Resources **resresources.nci.nih.gov**
- Funding **cancer.gov/researchfunding**

Centers, Networks, and Consortia
- Cancer Centers **cancer.gov/cancercenters**
- SPOREs **spores.nci.nih.gov**

National Clinical Trials Program
- Cancer Clinical Trials **cancer.gov/clinicaltrials** and **cancer.gov/clinicaltrials/understanding**

Bioinformatics for Cancer Research
- Center for Bioinformatics **ncicb.nci.nih.gov**

Genes and the Environment
- Family Registry **epi.grants.cancer.gov/CFR**
- Genetics Network **epi.grants.cancer.gov/CGN**

Signatures and Microenvironment
- CGAP **cgap.nci.nih.gov**
- EDRN **cancer.gov/prevention/cbrg/edrn**
- Director's Challenge **dc.nci.nih.gov**

Molecular Targets
- Developmental Therapeutics **dtp.nci.nih.gov**
- Intramural Initiatives **ccr.cancer.gov/initiatives**

Cancer Imaging and Molecular Sensing
- Biomedical Imaging **cancer.gov/bip** and **cancer.gov/clinicaltrials/understanding/science-explained-imaging**

Cancer Communications
- Extraordinary Opportunity **cancercontrol.cancer.gov/eocc**

Quality of Cancer Care
- Applied Research **appliedresearch.cancer.gov**

Cancer-Related Health Disparities
- NCI Center **crchd.nci.nih.gov**

Cancer Survivorship
- Survivorship Research **survivorship.cancer.gov**

Tobacco and Tobacco-Related Cancers
- Tobacco Research **tobaccocontrol.cancer.gov**

Research Training and Career Development
- Opportunities **cancertraining.nci.nih.gov**

Emerging Trends in Cancer
- Progress Report **progressreport.cancer.gov**
- Mortality Maps **cancer.gov/atlasplus**
- SEER **seer.cancer.gov**

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By email	cisocc@pop.nci.nih.gov
By Internet	cancer.gov/publications
By phone	1-800-4-cancer
By fax	1-301-330-7968

Telephone Assistance for Smoking Cessation

Through the Cancer Information Service (CIS) at 1-800-4-CANCER, NCI provides telephone-based assistance for smokers who want to quit. Callers in the United States, Puerto Rico, the U.S. Virgin Islands, and territories in Guam and Saipan can speak with someone in English or Spanish.

Smoking cessation service representatives:
- Assess the caller's individual smoking behavior.
- Provide brief educational messages.
- Help callers develop a personalized action plan for quitting.
- Reinforce the information with written materials.

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