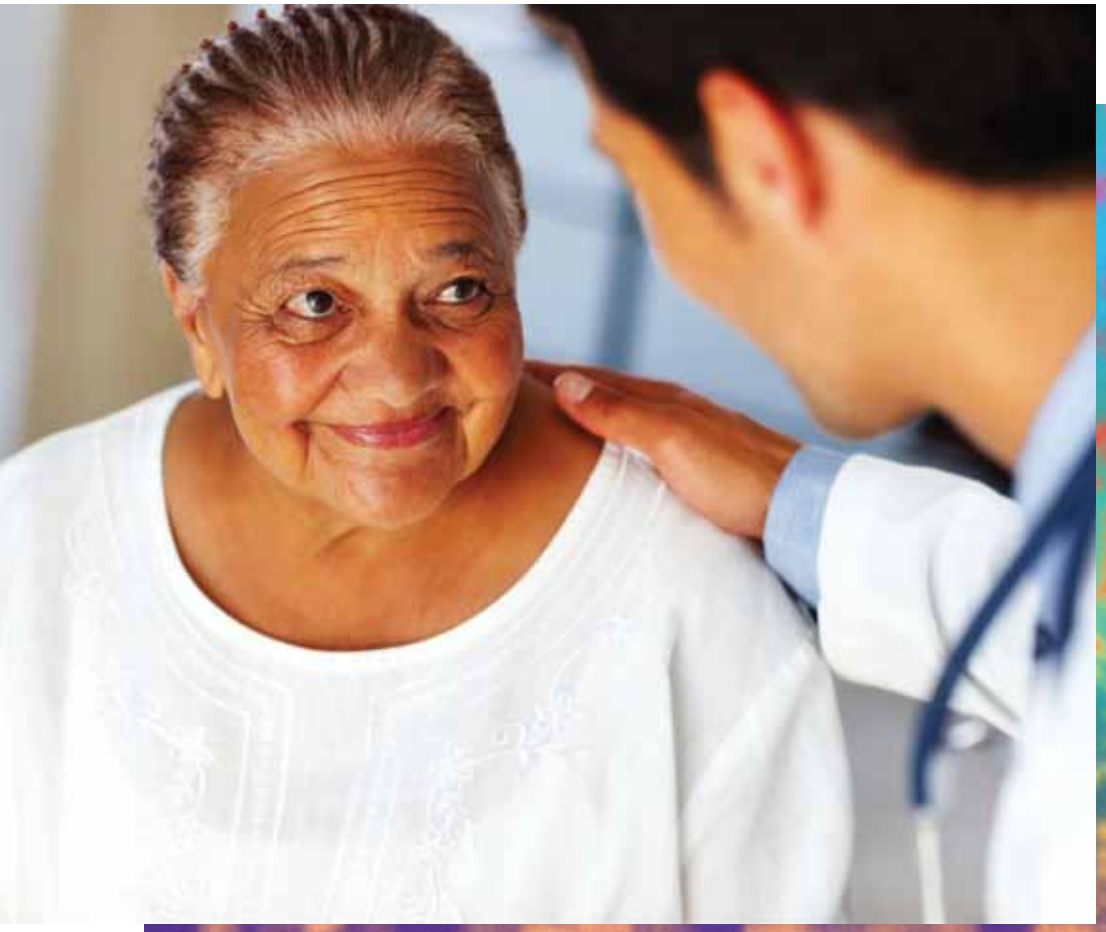
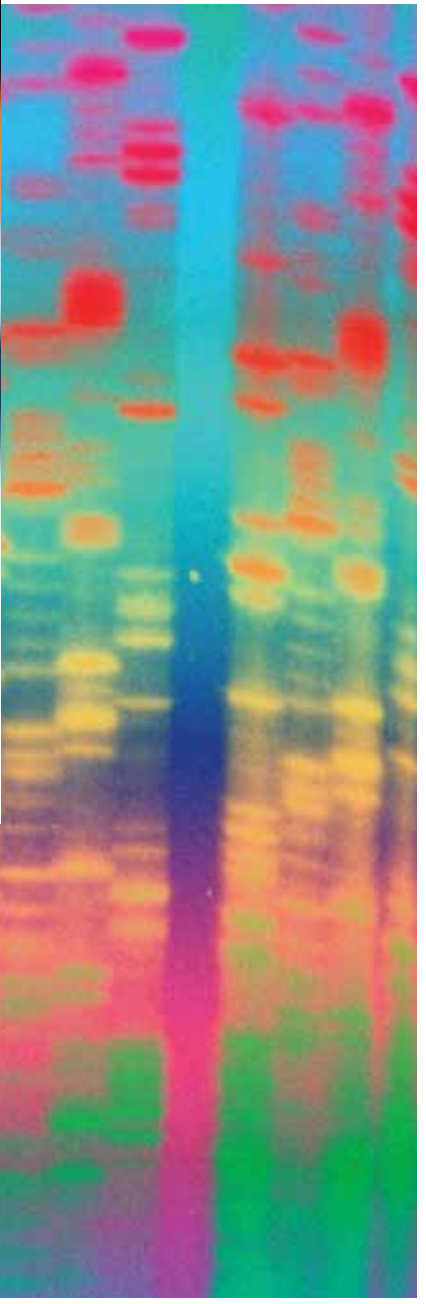
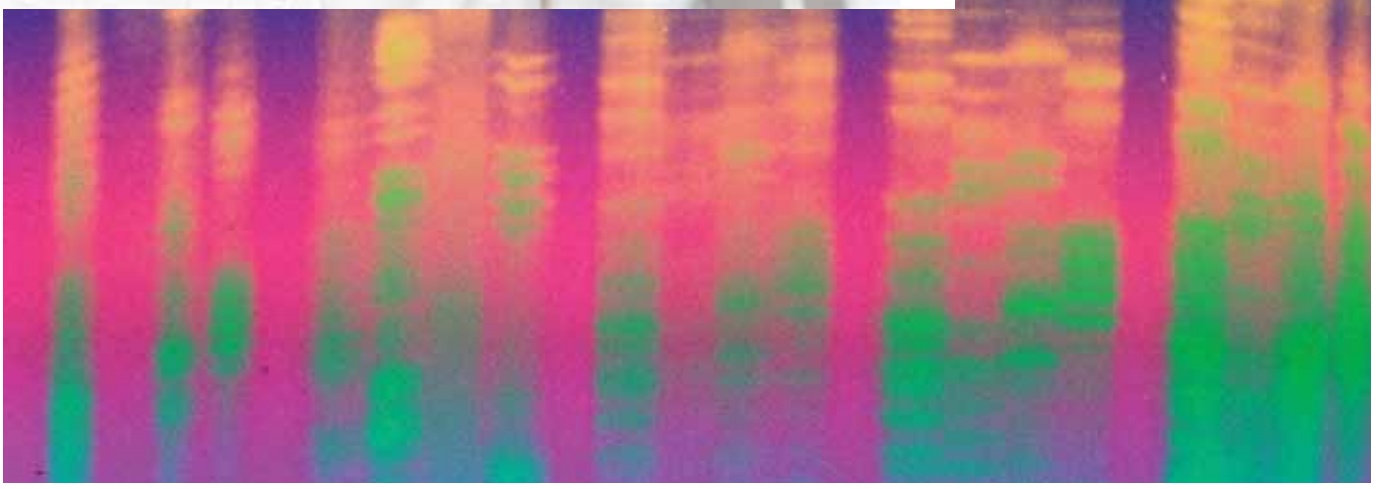
Building on Opportunities in Cancer Research

NATIONAL CANCER INSTITUTE

AN ANNUAL PLAN AND
BUDGET PROPOSAL FOR
FISCAL YEAR
2016

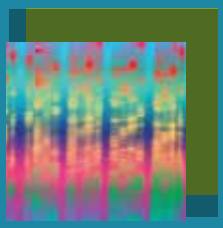


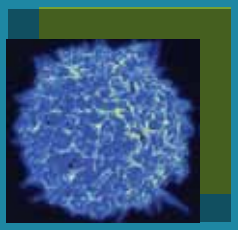




U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Table of Contents





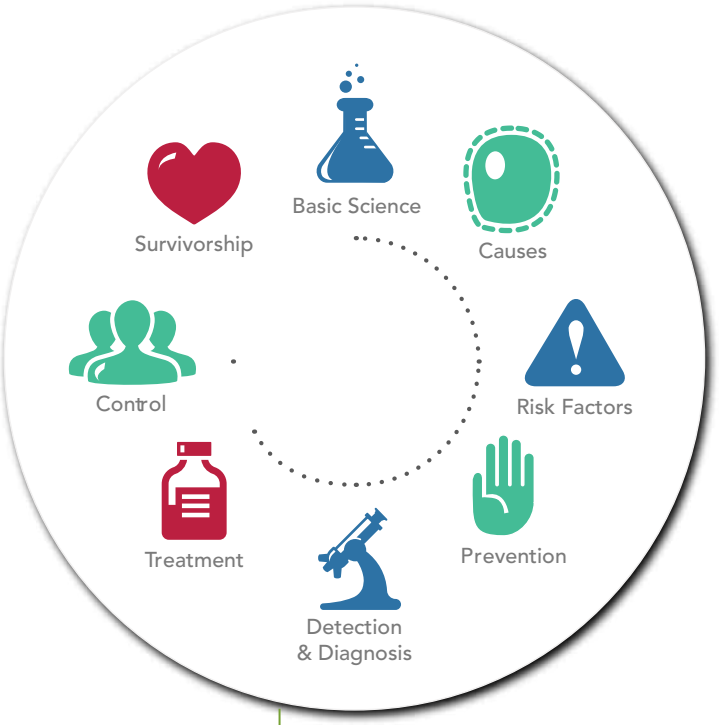
This is a time of remarkable opportunity in cancer research.

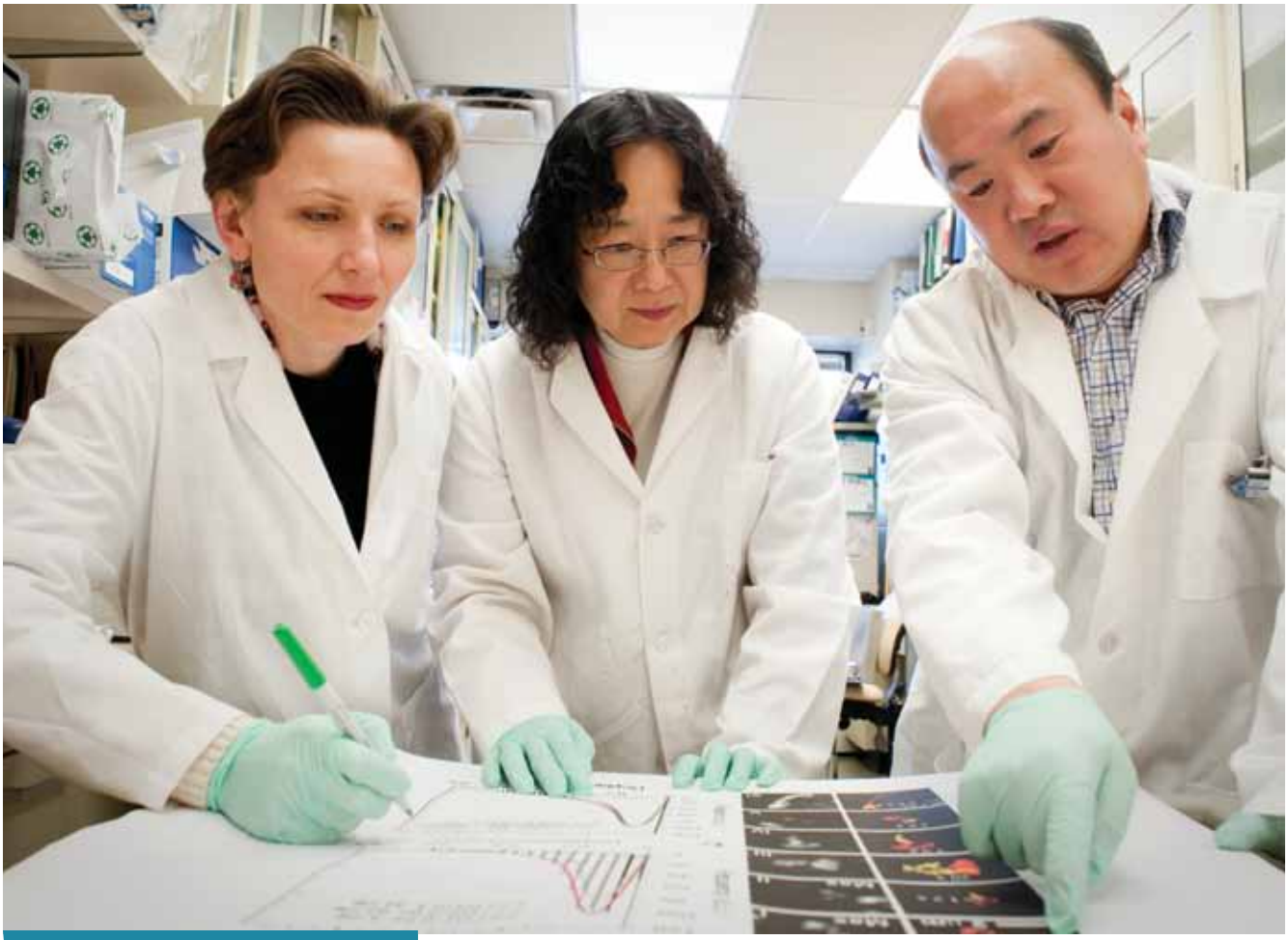
Armed with broad knowledge about how various kinds of cancer arise and with powerful new research tools, the cancer research community, under the leadership of the National Cancer Institute (NCI), is poised to reduce the burden of cancer in this country and around the world at an accelerated pace.

The NCI's goal is to support research that ultimately leads to important clinical outcomes: improvements in prevention, diagnosis, and treatment that can reduce the incidence, morbidity, and mortality of all types of cancer. Making sustained progress, however, requires a wide range of research disciplines that span the continuum from basic science to clinical research to research on implementation and cancer care delivery.

They include a variety of basic sciences, such as genetics, genomics, cell biology, immunology, and nanotechnology; translational and clinical sciences, such as drug development and testing, diagnostics, and the discovery and development of molecular markers, advanced imaging technologies, and new radiotherapy techniques; population sciences, such as population genetics, epidemiology, and environmental sciences; and behavioral sciences. Virtually all major advances toward the goal of improving the prevention, diagnosis, and treatment of cancer depend on many kinds of science. Cancer research is also cumulative. Today's investments in basic science will provide tomorrow's opportunities in clinical research.

NATIONAL CANCER INSTITUTE
SCOPE OF OUR WORK





The NCI seeks to manage its resources to take advantage of the most promising scientific opportunities. Photo of NCI researchers Olga Nikolaitchik, Ph.D., Wei-Shau Hu, Ph.D., and Jianbo Chen, Ph.D.

Photo by Rhoda Baer

The NCI's broad responsibilities for supporting research are severely tested during fiscally austere times that require a delicate balancing of its resources. This is especially true during long periods when budgets do not keep pace with inflation, as has occurred over the past decade. (The temporary budget increases in 2009 and 2010 associated with the American Recovery and Reinvestment Act [ARRA] were exceptions to this trend.) NCI-supported activities include funding thousands of grants to individual scientists and teams in many fields; supporting a national infrastructure for clinical research; training the next generation of researchers in diverse disciplines; and maintaining the NCI-Designated Cancer

Today's **investments in basic science** will provide tomorrow's **opportunities in clinical research**.

Centers and the NCI intramural research program. The NCI is attuned to the changing understanding of cancer and seeks to manage its resources to take advantage of the most promising scientific opportunities. Yet, despite careful management, current budget limitations mean that many meritorious research proposals, including some proposing bold concepts, must still go unfunded each year.

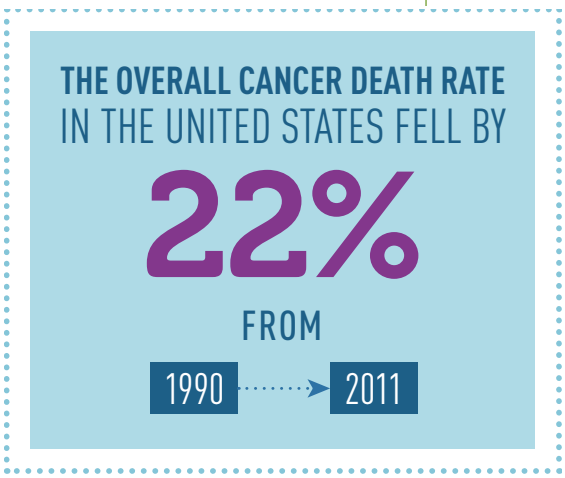
The following pages provide examples of the scientific opportunities before us. You will see that exciting progress is being made. But, for the many Americans diagnosed with cancer each day, progress is not being made quickly enough.

Harold Varmus, M.D.
Director, National Cancer Institute

Photo by Matthew Septimus

Lower Death Rates & More Survivors

Trends in cancer-related mortality are an important measure of the impact of cancer research, because they provide an overall assessment of what is happening to the combination of cancer incidence, treatment, prognosis, and outcome. Before 1990, overall age-adjusted cancer mortality rates increased for several decades. Since the mid-1990s, however, they have dropped steadily. Part of this sustained success in reduced cancer mortality is attributable to recognition of the harms caused by tobacco, which has led to reductions in tobacco consumption in the United States. This reduced consumption has lowered the overall risk of and deaths from tobacco-related diseases, including the most common forms of lung cancer, which claim more lives among both men and women than cancers in any other organ. Mortality rates are also decreasing for most other cancers, including those occurring at the three most common sites: the breast, colon/rectum, and prostate.

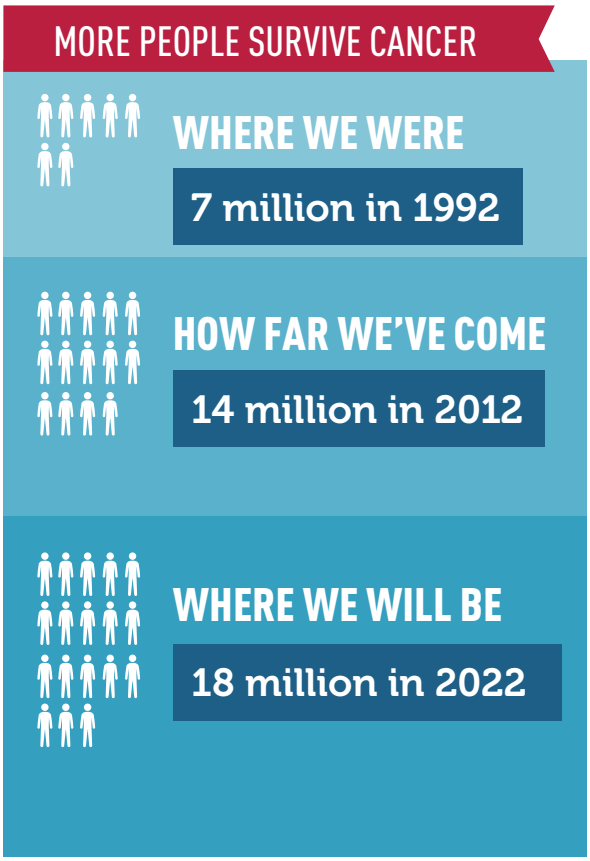


Source: SEER Cancer Statistics Review 1975-2011.

These improvements in mortality rates have been accompanied by a substantial increase in the number of cancer survivors. The number of people living beyond a cancer diagnosis in the United States doubled during the 20-year period between 1992 and 2012, from 7 million to 14 million, and is expected to rise to 18 million by 2022. Thus, whereas cancer survivors accounted for about 2.5 percent of the U.S. population in 1992, it is estimated that cancer survivors will account for more than 5 percent of the population in 2022. Importantly, many of these cancer survivors will return to live active and productive lives following their cancer diagnosis. But for many of these survivors, long-term effects, both physical and psychological, may remain. Recognizing this, survivorship research remains a key component in the research portfolio of the NCI.

It is estimated that **cancer survivors** will account for **more than 5 percent of the population in 2022.**

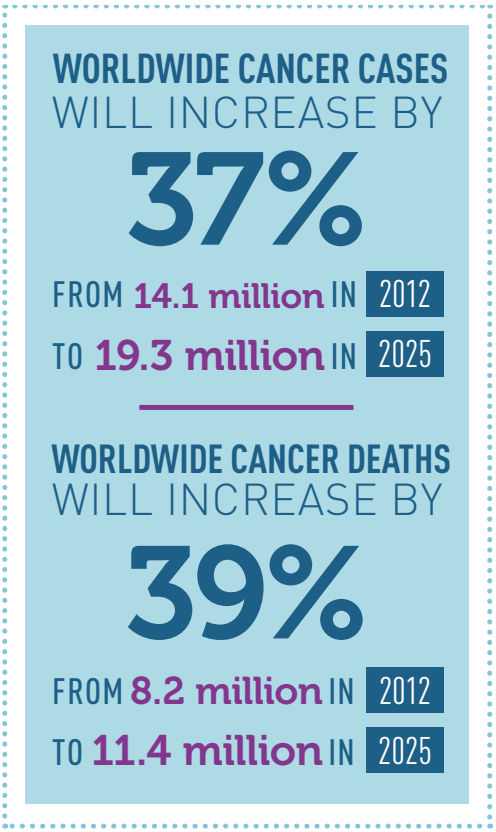
Despite these advances, too many people still face a cancer diagnosis, and far too many are still dying from the disease. It is estimated that more than 600,000 people in the United States will die from cancer in 2014 and that there will be more than 1.6 million new cases. In addition, our progress in preventing, diagnosing, and treating cancers is not universal for all forms of the disease. The mortality rates for some cancers have actually increased. For example, death rates from liver cancer increased by about 20 percent between 2001 and 2010. Thus, much work remains.



Source: de Moor JS, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers* Prev. 2013; 22(4):561-570.

Because older age is a major risk factor for developing cancer, improved life expectancy by itself will lead to a rise in the total number of cancer cases in the United States. Therefore, although the age-adjusted rates at which cancer develops are expected to continue to decline, the aging of the U.S. population means that the total number of cancers will increase. Between 2012 and 2025, the estimated number of cancer cases will increase by 31 percent, from 1.6 million to 2.1 million; the estimated number of cancer-related deaths will increase even faster, by 37 percent, from 620,000 to 850,000. These projected increases imply that intensive and sustained research efforts against cancer will continue to be critical. The NCI continues to employ every aspect of its portfolio to better prevent, diagnose, and treat cancer, but these efforts must be enhanced to keep up with the changing demographics of our society.

Over the past few decades, the incidence of obesity has risen markedly in the United States and in many other countries around the world. Although the so-called "obesity epidemic" has been most commonly linked to the rising incidence of diabetes and related conditions, it also has substantial implications for cancer research and cancer control, since obesity is associated with increased risks of developing cancer at many sites. These sites include the esophagus, endometrium (uterus), colon/rectum, pancreas, breast, and liver. In the liver, nonalcoholic steatohepatitis, which can develop in obese individuals, is associated with an increased risk of developing liver fibrosis and liver cancer. It is important to refine our understanding of the associations between



Source: Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013.

obesity and specific cancers, determine the mechanisms underlying these associations and their potential reversibility for people who lose weight, and support behavioral research to help overcome obesity at the individual and population levels.

Improvements in nutrition, health care, and other factors are increasing life expectancy for most of the world. However, this benefit is accompanied by an increase in many diseases associated with an aging population, including cancer, and this trend is being exacerbated by greater tobacco consumption in many low- and middle-income countries. The International Agency for Research on Cancer, part of the World Health Organization, estimates that there will be 19.3 million cases of cancer worldwide in 2025, a 37 percent increase over the 14.1 million cases in 2012. During that time span, the estimated number of cancer-related deaths worldwide will increase by 39 percent, from 8.2 million to 11.4 million.

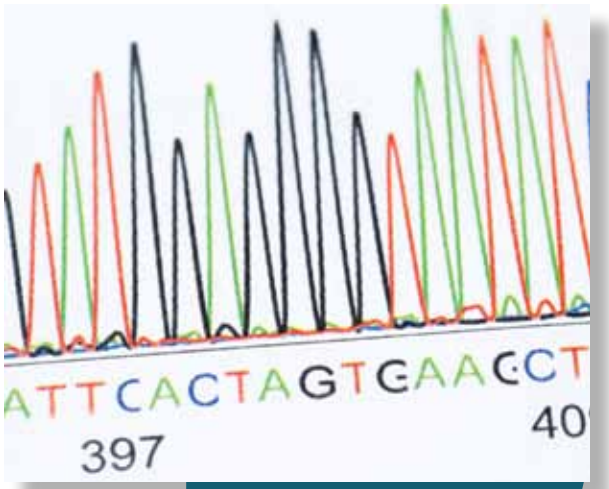
To help address this expanding global burden of cancer, the NCI established its Center for Global Health (CGH) in 2011. The center facilitates global collaboration by leveraging research resources with U.S. government agencies, foreign governments, nongovernmental organizations, and pharmaceutical and biotechnology companies to support clinical trials and device development appropriate for low- and middle-income settings.

Improved Prevention, Screening & Treatment

Basic science: Uncovering clues for tomorrow's cancer prevention and treatment. Cancers are disorders of cell growth, cell survival, and other cell behaviors, fueled largely by changes in cell chromosomes. Therefore, the NCI has traditionally made substantial investments in many fundamental aspects of cell biology and genetics, recognizing that basic biological science is essential in efforts to understand this set of diseases.

That premise has not changed, and the NCI continues to put resources toward many exciting areas of basic science under investigation. For example, we have known for several decades

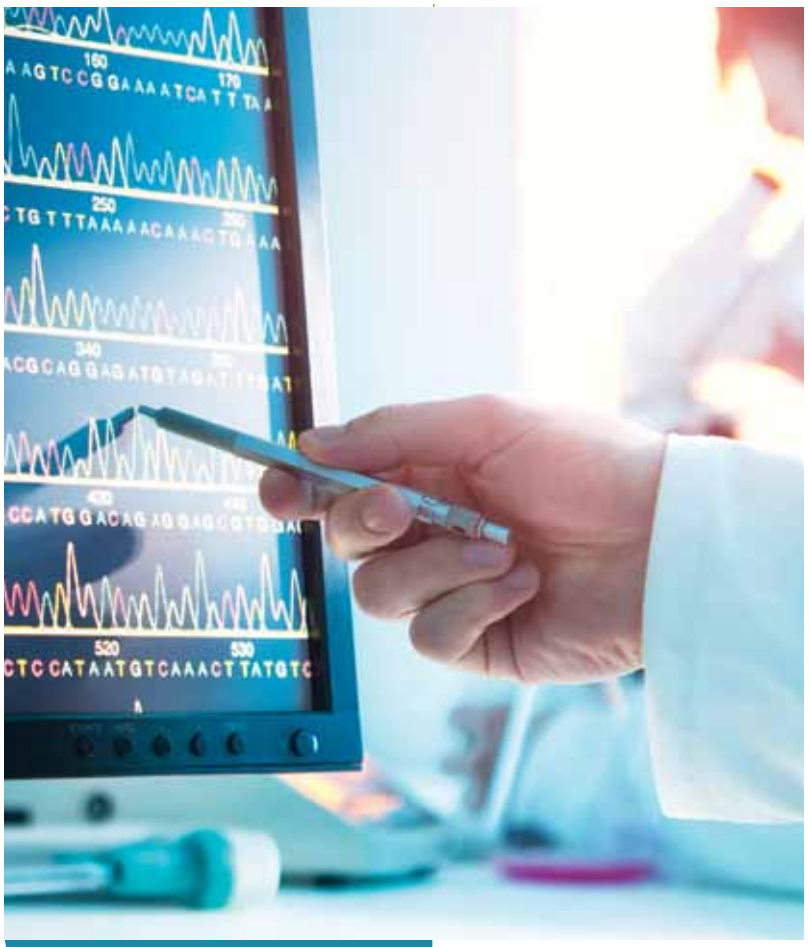
that much of a cell's RNA comprises the messengers that instruct the cell to make its proteins, but unexpected developments in just the past decade have demonstrated compellingly that the cell has other forms of RNA that cannot be translated to make proteins. Instead, they directly regulate the expression of many, if not all, genes that do encode proteins. Many of these regulatory "non-coding" RNAs can influence the behavior of cancer cells. Their roles in cancer, as well as the roles of other regulators, such as proteins that govern gene expression, are still under intense investigation. The dividends of that research may be a more profound understanding of how a normal cell becomes a cancer cell, as well as new ways to classify and treat cancers.



DNA sequencing results from an automated DNA sequencing machine.

Abnormalities of metabolism, which have been identified in many tumors, also represent an important area of basic and applied research. The affected genes, which are fundamental regulators of the normal energy balance of the cell, are mutated in several forms of cancer. One class of these mutant genes has been identified in several forms of brain tumors and in acute myeloid leukemia. Another class has been found in hereditary and nonhereditary forms of kidney cancer. These changes in energy metabolism, which contribute to the abnormal growth properties of the cancer cells, are being intensively studied to better define their mechanism of action and their role in cancer to determine whether their inhibition might be clinically beneficial.

From the earliest days of cancer research, much of our knowledge about this set of diseases has come from studies in experimental models, using cells grown in Petri dishes and animals that develop cancer naturally or after experimental manipulation. Over the past couple of decades, novel genetic methods have been used to create mice that develop cancer in a predictable way in a variety of tissues under the influence of mutant genes also found in human cancers of the same type. Refinements in the methods used to generate mouse models of cancer are making them more closely related to human disease, and technological advances are making it easier to study the consequences of specific gene mutations and potential therapies in these models. The evaluation of tumors that are taken directly from patients and placed immediately in mice (patient-derived xenografts) is enabling the study of these tumors in the context of an experimental animal. In addition, three-dimensional methods for growing cancer cells



A researcher analyzing DNA sequencing results.

in culture enable researchers to study tumor architecture that more closely mimics that found in the tumor environment in living animals or patients than that provided by traditional two-dimensional culture methods. These advances have considerable potential to provide additional insight into the development of cancer, the role of the extracellular matrix in which tumors grow, and responses to new therapeutic interventions.

It is generally agreed that cancers arise from single cells that continue to accrue mutations during the course of a multiyear process of tumor evolution. Thus, it was not unexpected when the analysis of tumor genomes from different parts of a cancer, either metastatic growths or cells from different locations in the primary tumor, revealed significant heterogeneity and important aspects of the cancer's evolutionary process. This heterogeneity has important implications for understanding the biology and evolution of tumor development and progression, as well as for treatment with conventional therapies, targeted drugs, and immunotherapies.

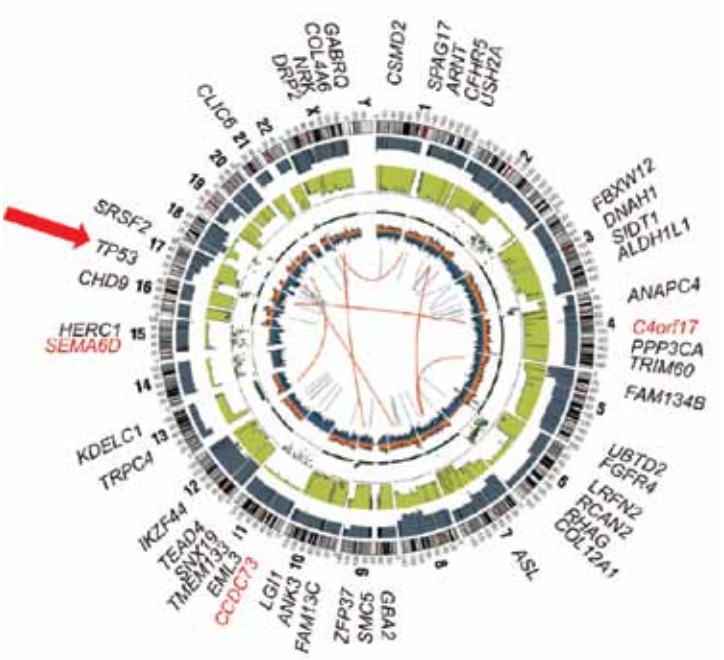
Our understanding of the tumor microenvironment, which is composed of the noncancerous cells and other materials that surround cancer cells in a tumor mass, has recently increased. We now recognize the importance of immune cells, blood vessels that support tumor growth, and other factors, such as hormonal mediators of cell growth and extracellular matrix proteins that influence tumor cell migration and tumor architecture. Additional study of the components of the microenvironment and their interactions with the tumor has considerable potential for improving our understanding of the interplay between tumors and their hosts. These interactions are likely to be complex but profound and may hold clues for future efforts at prevention and treatment.

Cancer: Genetics plus environmental exposures.

A wealth of research, much of it supported by the NCI, has determined that cancer develops through a complex interplay of genetic and environmental factors. In some cases, the risk of developing cancer is strongly influenced by inheriting a mutation in a single gene, such as *BRCA1* or *BRCA2.* Mutations in these genes confer a high risk of familial breast and ovarian cancer. More commonly, however, the genetic background of individuals plays a more subtle role in the risk of cancer. Although their genes can make important contributions to cancer susceptibility, the sum of their exposures to various environmental factors is believed to account for the development of most cancers. Many environmental factors can contribute to cancer risk, including tobacco use, some types of infection, exposure to ultraviolet light, and lifestyle factors, such as obesity, lack of exercise, and eating an unhealthy diet.

Once these risks and exposures are identified and understood, we can frequently develop effective preventive interventions. Interventions may include reducing cancer risk in the general population or identifying high-risk individuals who can be screened for signs of precancers or early cancers, which can often be treated more effectively than advanced disease. Reducing exposure to an environmental carcinogen, such as tobacco, asbestos, or ultraviolet light, is one approach. Another is to reduce the consequences of exposure to the carcinogen. This approach includes vaccinating against hepatitis B virus (HBV) and human papillomavirus (HPV), and using sunscreens that block ultraviolet light. Reducing exposure can also be employed in some instances of familial predisposition to cancer. In women who have an abnormal *BRCA1* or *BRCA2* gene, preventive removal of the breasts, ovaries, and fallopian tubes decreases their risk of developing cancer at these sites. Tailored screening approaches may also be employed. For example, individuals who are considered to be at high risk of colorectal cancer because of a familial genetic abnormality are recommended to start colorectal cancer screening at an earlier age than people in the general population.

Cancer: A disease of abnormal genes and their activities. At the level of the tumor, cancer is often described as a "genetic disease" because the tumor cells have undergone one or more irreversible changes in some genes. These changes may arise from mutation of the genes, which increases or decreases their activity; an increase in the number of copies of certain genes, which often increases their activity; deletion of parts or all of some genes, which usually abolishes their activity; or rearrangements between two genes, which lead to the production of fusion proteins that have increased activity. These genetic changes are critical to the development of the tumor, and they continue to be important as the tumor grows. Changes designated as "epigenetic" also contribute to cancer, usually by increasing or decreasing the expression of specific genes by chemically modifying DNA or the proteins associated with DNA. These changes are called "epigenetic" because the chemical modification and consequent alterations in gene expression are potentially reversible, in contrast to the irreversible nature of changes in the sequence or organization of genes.



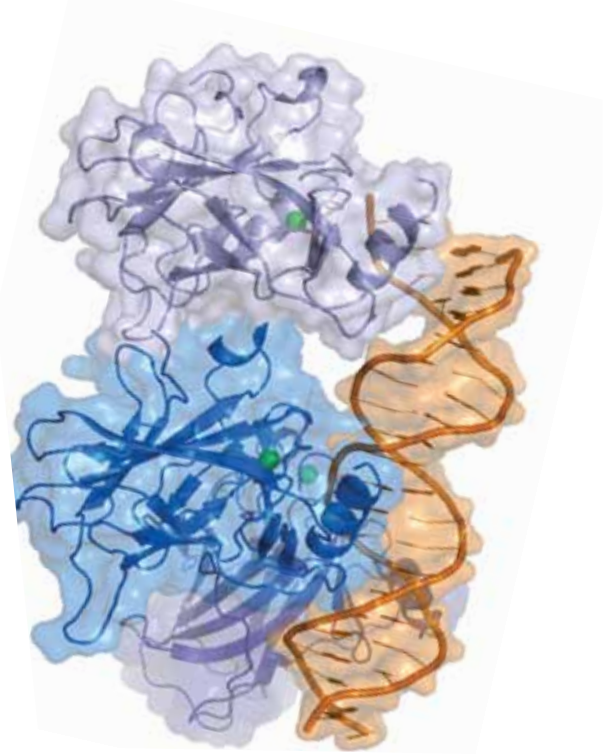
Tumor cells have undergone irreversible changes in one or more genes. This graphic visualization shows the genetic alterations in a human rhabdomyosarcoma tumor.
Image by Javed Khan, M.D.

At the level of the tumor, **cancer is often described as a "genetic disease"** because the tumor cells have undergone one or more irreversible changes in some genes.

At least two types of functional genetic and epigenetic changes contribute to the progression of a normal cell into a cancer cell. One involves genes with the natural capacity to prevent the development of cancer; many of these genes are referred to as tumor suppressor genes, whereas others in this category promote the repair of damaged DNA. Changes that affect this class of genes reduce the cell's ability to block abnormal growth. The second type of

change involves genes that have the capacity to promote the development of cancer. Many of these genes are referred to as oncogenes, and their alterations in cancer increase their activity. Both types of changes occur in the vast majority of malignant tumors.

It is also recognized that a person's inherited genes may contribute to tumor susceptibility. An unfortunate, but dramatic, example of this situation is seen in individuals whose inherited DNA has a mutation that inactivates one of the two copies of the *RB1* tumor suppressor gene. When this happens, all of the individual's cells have one copy of this inactivated version. The patients are usually healthy when born because they have one fully functioning copy of the gene in their cells, in addition to the inactivated copy. During early childhood, however, these individuals have a high risk of developing retinoblastoma if their one normal copy of *RB1* in a retinal cell also becomes inactivated. This inactivation process may arise independently in more than one retinal cell, leading to the development of separate tumors in each eye. If the inactivation occurs in some other cells elsewhere in the body, tumors may develop at these locations.



A molecular model of a dimer of the p53 tumor suppressor protein bound to DNA.
Image by Thomas Splettstoesser

Targeting specific genes in cancer treatment.
Understanding the molecular changes in cancer has stimulated efforts to develop drugs that specifically target key proteins involved in the development of a given cancer type. This therapeutic approach is often referred to as precision medicine. Although surgery, radiation therapy, and standard chemotherapeutic drugs continue to have an important role in cancer treatment, our increased understanding of the genetic and epigenetic changes in cancer, together with our

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evolving ability to intervene, present the opportunity to provide treatments that are potentially less toxic and more effective than previous therapeutic approaches. Another aspect of precision medicine is the development of assays, often called companion diagnostics, that can predict which patients are most likely to benefit from a particular targeted therapy. For example, the Food and Drug Administration (FDA) approval of vemurafenib (Zelboraf) for patients with advanced melanoma whose tumors harbor a frequent mutation in the *BRAF* oncogene came with a requirement that the mutation be identified by an FDA-approved companion diagnostic test before the drug is used.

Most targeted drugs are directed at inhibiting the proteins encoded by oncogenes because it is currently technically easier to inhibit these proteins than it is to replace the missing activities of tumor suppressor genes. Thus far, most of the successful monoclonal antibodies and small molecule drugs inhibit the activities of oncogene-encoded proteins. Examples include erlotinib (Tarceva), which targets the epidermal growth factor receptor (EGFR), for the treatment of lung adenocarcinoma; trastuzumab (Herceptin), which targets ERB-B2 (also known as HER2), a receptor that is similar to EGFR, for breast cancer treatment; and imatinib (Gleevec), which targets a fusion protein resulting from a rearrangement between two genes, for the treatment of chronic myelogenous leukemia. In contrast to therapeutic approaches that target specific abnormalities in the cancer cell, an alternative successful approach is to harness the potential of the patient's own immune system to seek and destroy the cancer cells. This approach is discussed in the section titled *Harnessing the Promise of Immunotherapy*.

The genomic analysis of tumors, which examines the genes in tumor cells and may compare the differences between the patient's normal cells and changes found in the tumor cells, has revealed a potential challenge for therapy, namely, that the spectrum and number of changes that can lead to cancer are so great that it is difficult to identify the specific genetic and epigenetic changes responsible for driving the abnormal growth of the tumor cells. Fortunately, however, changes in some oncogenes have been found to occur repeatedly in a given type of cancer, and abnormalities that involve the same gene often occur in more than one cancer type. Therefore, if drugs that target a particular abnormal gene are useful in one form of cancer, they will often be useful in the treatment of other types of cancer that have the same abnormal gene.

Classifying cancers according to their genomic profiles.
Effective cancer treatment can be directed against the specific genetic abnormalities in a tumor. Therefore it is more and more important to determine the genomic profile of a cancer and to classify the cancer according to that categorization, rather than just by the organ site where it developed or by its appearance under a microscope. Such categorization is important both for cancer treatment today and for research that can lead to new treatments that will improve the outcome for patients with cancer in the future. For example, genomic profiles can be used in basic research that seeks to understand which genetic abnormalities are most critical to a tumor, and these findings can help to prioritize efforts aimed at identifying drugs that target specific genes. This analysis can also deepen our basic understanding of how specific combinations of abnormal genes collaborate in cancer. Such understanding is likely to lead to improved combinations of targeted treatments for cancer and to help prevent and overcome drug resistance, which, unfortunately, occurs commonly with targeted treatment by a single drug.

Illustration of the DNA double helix and the genetic code.
Image from the National Human Genome Research Institute

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Rapid Progress Depends on Long-Term Support

Supporting research improves health. The NCI is committed to answering the most pressing questions about each type of cancer and to continuing the pursuit of fundamental knowledge about the inner workings of cancer cells, so that we can eventually prevent and control cancers of all types. As indicated previously, investigators and, increasingly, patients with cancer are benefitting from new—but often costly—research methods used in genomics and informatics. These approaches include drug screening and development; cancer detection, diagnosis, and monitoring; and immunologically and genetically based therapeutics. The NCI is committed to bringing improved, less-toxic, and less-debilitating treatment to patients, based on the molecular abnormalities of their disease.

Increased funding is associated with faster progress. Important gains made over the last four decades have occurred as the cancer research enterprise has expanded in talent, facilities, and ideas. The rapid escalation of the NCI budget following the National Cancer Act of 1971 and the doubling of the National Institutes of Health (NIH) budget over a 5-year period that began in the late 1990s contributed to these gains. These two periods of rapid growth were remarkably fruitful. The first period of growth launched the pursuit of cancer genes and the molecular basis of oncogenesis, laying the foundation for the transformation of clinical oncology that is now occurring. The second period of growth accelerated completion of the human genome project, which led to current genomic analyses that now help guide the study and control of many diseases, including cancer.

Cancer research also benefitted significantly from the American Recovery and Reinvestment Act (ARRA) of 2009. The NCI saw an infusion of approximately $1.25 billion from ARRA, allowing the expansion of initiatives such as The Cancer Genome Atlas (TCGA) project, a joint effort by the NCI and the National Human Genome Research Institute (NHGRI) to catalog all of the genetic changes in more than 10,000 cancer cases involving more than 30 different types of cancer. TCGA and projects like it are providing a foundation for further discovery by the research community and stimulating new approaches to preventing, diagnosing, and treating cancer. Without the leadership and financial investment of the NCI, projects such as these would likely not occur or would be of smaller scale and progress at a slower pace.

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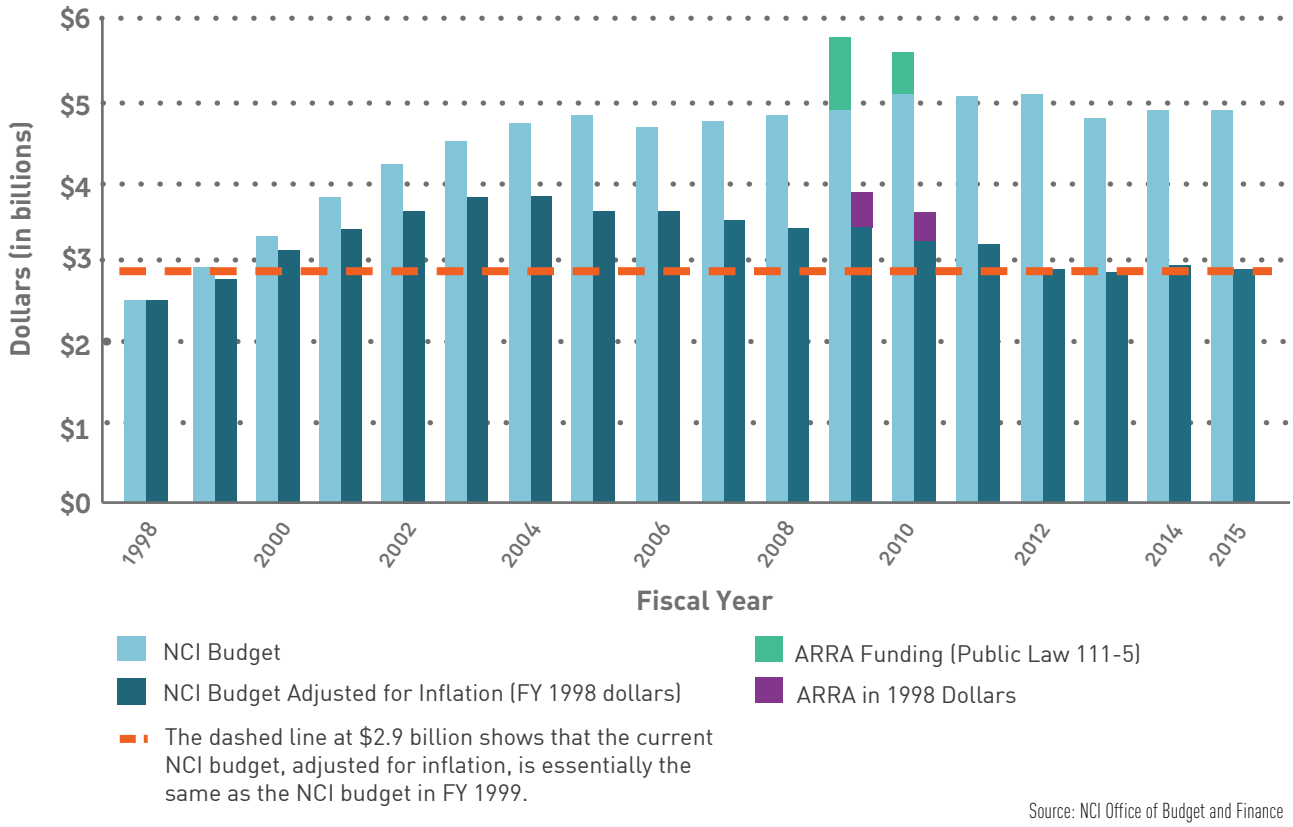
Flat budgets threaten short-term and long-term progress. Since 2003, with the exception of the funding received through ARRA, there has been a decade-long hiatus in financial growth in the nation's investment in research. Coupled with the increased expense of research and the loss of nearly 25 percent of the NCI budget in constant dollars since 2003 due to inflation, our ability to exploit some promising opportunities and to sustain rapid momentum in preventing, diagnosing, and treating cancer is being compromised. The current financial status of the cancer research enterprise has created an unhealthy, hypercompetitive atmosphere for both experienced and new investigators, who are vying for part of a progressively shrinking budget. In this climate, because the success rate of grant applications has dipped so low, substantially more time must be devoted to preparing grant applications and to keeping laboratories afloat, which reduces scientific productivity and threatens promising careers. A larger sustained budgetary commitment to cancer research would be a visible step to attracting and retaining the scientists we need to pursue the many opportunities before us.

Without the leadership and financial investment of the NCI, projects such as [TCGA] would likely not occur or would be of smaller scale and **progress at a slower pace.**

THE DECLINING PURCHASING POWER OF THE NCI BUDGET



Source: NCI Office of Budget and Finance

The NCI supports the National Cancer Program in various ways, both financially and intellectually. It provides resources to individual investigators and to institutions, provides leadership to national infrastructures that care for patients and that develop new methods to prevent and treat disease, and conducts research in especially challenging areas. Over the last 10 years, the core support that the NCI has been able to provide to the nation's cancer research enterprise has eroded. Years of trimming around the edges have resulted in an NCI that funds too few grants. The grants that are funded are too small to adequately cover the costs of clinical trials and sufficiently support essential elements of the enterprise, such as the NCI-Designated Cancer Centers. In short, we are underserving the cancer research community.

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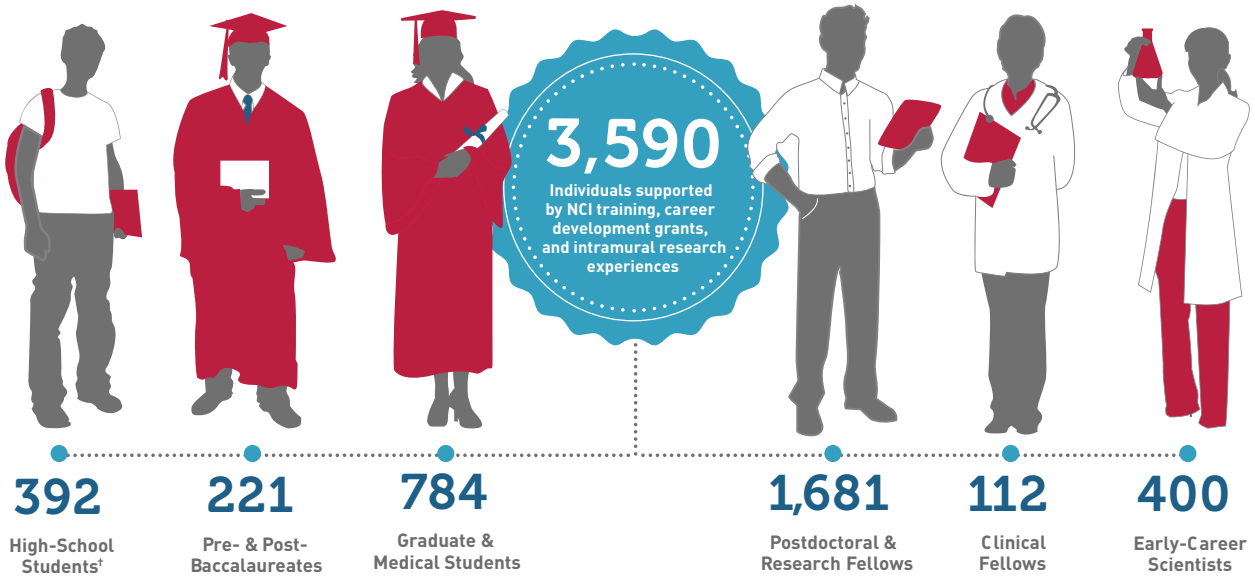
New Approaches to Funding Researchers

The NCI continues to develop new funding opportunities that adapt to changes in the way that science is conducted. Support for the best science underpins everything the NCI does; therefore, supporting the best scientists is paramount. Today, attracting the best minds to the field of cancer research is challenging. Retaining talent is also difficult. The uncertainty of a successful career in cancer research due to a lack of funding opportunities is a significant barrier to embarking on, and remaining in, this career path. The NCI is committed to supporting the training and development of a strong workforce of cancer researchers that spans the career continuum. However, in the current hypercompetitive culture of biomedical science, the early careers of graduate students, postdoctoral fellows, and

NATIONAL CANCER INSTITUTE
Training the Workforce

In FY 2013, NCI supported 3,590 emerging cancer researchers through training and career development grants and intramural research experiences.*



* Numbers do not include students and postdoctoral fellows supported by NCI research project grants, cancer center grants, and other non-training mechanisms

† Does not distinguish between summer research experiences and part- or full-time appointments

young investigators may be hampered by low salaries, many years spent in training positions, and still more years in an independent research position, before they obtain NIH funding for their research. For most of the past 50 years, at least 30 percent of grant applications were funded, dipping to 25 percent during periods of lean budgets. Today, the percentage of successful applications hovers in the mid-teens, far lower than at any other time. Although the NCI is actively building a cancer research workforce for the future, these efforts will appear hollow without strong support for funding these young scientists. This infrastructure problem is not limited to cancer research.

Even established researchers are forced to devote too much time to securing funding rather than conducting research or training the next generation of scientists. To partially address this problem, the NCI recently established the Outstanding Investigator Award. This new R35 funding mechanism is designed to provide longer-term support—7 years—and more than twice the dollar amount

The NCI is committed to supporting the training and development of **a strong workforce** of cancer researchers **that spans the career continuum.**

Examples of NCI Grants

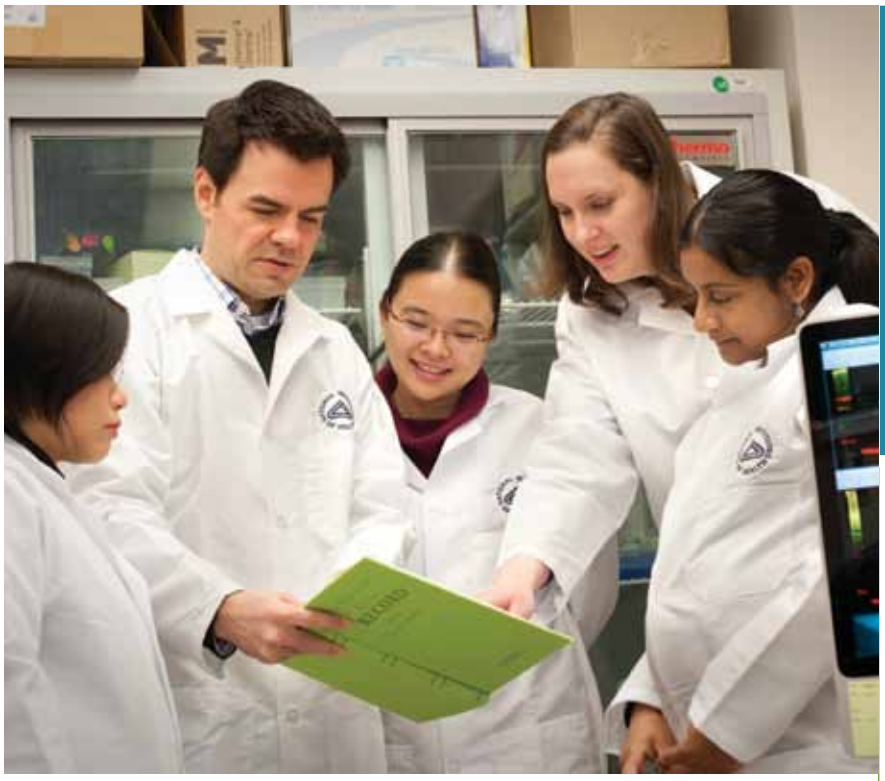
R01: Research Project
These grants are awarded to institutions to allow a Principal Investigator to pursue a scientific focus or objective in his or her area of interest and competence. Applications are accepted for health-related research and development in all areas within the scope of the NIH's mission.

R21: Exploratory/ Developmental Grants
These grants encourage the development of new research activities in categorical program areas. Support generally is restricted in level of support and duration.

R35: NCI Outstanding Investigator Award
This new award supports investigators with outstanding records of productivity and allows them to embark on long-term projects of unusual potential in cancer research.

of an average R01 investigator-initiated grant to experienced investigators who are likely to continue to conduct seminal cancer research as well as to mentor the next generation of cancer researchers. With this support, investigators may pursue research that might be viewed as too high-risk to be funded through regular grant mechanisms. In addition, through mechanisms such as R21 exploratory grants, the NCI seeks to help investigators conduct other potentially new and exciting but high-risk studies. R21 grants are not substitutes for the main investigator-initiated grants, the R01 awards, because R21 grants are given for fewer years and have a lower level of annual funding. However, when used appropriately, the R21 awards can be useful for investigators who need additional data to successfully compete for larger grants. The need to maintain the vitality of the cancer research workforce cannot be overstated, and the NCI takes its leadership role in this domain very seriously.

Although traditional single-investigator-driven approaches remain preferable for a range of scientific endeavors, coordinated teams of investigators with diverse skills and knowledge have proven to be helpful in many areas of cancer research. As part of its commitment to improve the quality of cancer research, the NCI supports a variety of "team science" approaches, including those used in a large proportion of cancer genomics and cancer epidemiology research. This support of team science has yielded important discoveries but has also identified barriers to broader collaborations. Authorship of journal articles and the acknowledgment required for tenure decisions are two examples of issues that must be addressed to fully achieve the potential of team science. The NCI has led in this effort to appropriately recognize the contributions of individuals involved in interdisciplinary research. The NCI spearheaded a change in the NIH biosketch, which accompanies grant applications and documents the qualifications of the investigators applying for the grant. Instead of merely listing their most relevant publications, the new biosketch takes a narrative form that emphasizes individual accomplishments and their significance by asking investigators to enumerate their most important research accomplishments, the significance of the accomplishments, and their specific contributions to the research. The NCI has also created an online resource, the Team Science Toolkit (www.teamsciencetoolkit.cancer.gov), to help investigators support, conduct, and study team science. Professionals from many disciplines can connect



NCI researcher Joseph Ziegelbauer, Ph.D. (second from left), has teamed with the Trans-NIH RNA Interference Screening Facility and colleagues in the NCI HIV and AIDS Malignancy Branch to study the Kaposi sarcoma-associated herpesvirus.

Photo by Rhoda Baer

through the website, which provides a forum for sharing knowledge and tools to maximize the efficiency and effectiveness of team science initiatives.

The Provocative Questions initiative is another approach developed by the NCI to stimulate the research community and provide a new form of funding. This initiative has brought together researchers to identify questions in specific areas of cancer research that have been understudied, neglected, paradoxical, or difficult to address in the past. To encourage the NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways to answer some of these questions, select questions were advertised in requests for applications (RFAs), with a set-aside budget to fund the most meritorious applications. The selected questions have been categorized into five themes: cancer prevention and risk; mechanisms of tumor development or recurrence; tumor detection, diagnosis, and prognosis; cancer therapy and outcomes; and clinical effectiveness. To date, 168 grants have been funded with $63.9 million dollars to address the identified Provocative Questions.

THE PROVOCATIVE QUESTIONS INITIATIVE HAS IDENTIFIED QUESTIONS IN **CANCER RESEARCH** THAT HAVE BEEN UNDERSTUDIED, NEGLECTED, PARADOXICAL, OR DIFFICULT TO ADDRESS IN THE PAST.

THE INITIATIVE HAS FUNDED

168

GRANTS

WITH A TOTAL OF

$63.9

MILLION

Source: NCI Center for Strategic Scientific Initiatives

NCI-Designated Cancer Centers

The NCI-Designated Cancer Centers program is one of the anchors of the nation's cancer research effort. The 68 cancer centers, which are located in 35 states and the District of Columbia, form the backbone of the institute's programs for studying and controlling cancer. Together, they represent the nation's single most important source of new insights into the causes of cancer and strategies for prevention, diagnosis, and treatment; the research proposals from their investigators account for about three-quarters of the successful investigator-initiated grants that are awarded, after stringent peer review, by the NCI.

NCI-DESIGNATED CANCER CENTERS

The 68 NCI-Designated Cancer Centers are at the forefront of NCI-supported efforts at universities and cancer research centers across the United States. The centers are developing and translating scientific knowledge from promising laboratory discoveries into new treatments for cancer patients. There are 20 cancer centers, 41 comprehensive cancer centers, and 7 research centers. For more information, visit www.cancer.gov/researchandfunding/extramural/cancercenters/about.

Source: NCI Office of Cancer Centers

At any given time, hundreds of research studies are under way at NCI-Designated Cancer Centers, ranging from basic laboratory research to clinical assessments of new treatments. Many of these studies are collaborative and may involve several research centers and other partners in industry and the community. In addition to conducting meritorious basic and applied research, the cancer centers deliver quality cancer care to patients and their families, including in communities with underserved and understudied populations.

Each NCI-Designated Cancer Center receives a core support grant from the NCI that funds the critical research infrastructure of the center, in addition to the funding received from individual competitive research grants and contracts with the NCI. The funding provided by the core grants is essential for the efficient conduct of research at the centers and for maintaining the nation's progress against cancer. The size of the core grants is relatively small in comparison with the return on investment and with the size of other NIH center grants, such as those that support the approximately 60 institutions that receive Clinical and Translational Science Awards (CTSAs). The specific amount for each cancer center has depended on a variety of factors, including the budget cycle, resulting in awards that do not entirely reflect the scientific quality or quantity of the research performed at the center or the size and complexity of the center itself. To address this inequity, the NCI plans to adjust the size of the core grants and to provide a closer link between these more appropriate parameters and the size of the grants.

The funding provided by the **core grants** is essential for the **efficient conduct of research** at the [NCI-Designated Cancer Centers] and for **maintaining the nation's progress against cancer.**

NCI's National Clinical Trials Enterprise

Clinical trials are supported by industry, private philanthropy, and through public funding. Each of these mechanisms can make important contributions to improved interventions for cancer control. The NCI has a long history of supporting both small early-phase trials as well as large-scale trials, many of which have led to changes in the standard of care. The NCI's National Clinical Trials Network (NCTN) includes an active network of researchers, cancer centers, and community physicians. The program enrolled between 19,000 and 20,000 participants in clinical trials in 2014. With the involvement of more than 3,100 institutions and 14,000 clinical investigators, the NCI's clinical trials enterprise has changed the face of clinical oncology, establishing the safety and efficacy of many therapies now commonly used to treat patients with cancer.

People with cancer now live longer lives in part because of strategies that have come from the NCI's clinical trials program. For example, this year a clinical study found that adults with low-grade glioma, a type of brain tumor, who received chemotherapy following the completion of radiation therapy lived significantly longer than patients who received radiation therapy alone. In addition, early results from another clinical trial showed that men with hormone-sensitive metastatic prostate cancer who received the chemotherapy drug docetaxel (Taxotere) at the start of standard hormone therapy lived longer than patients who received hormone therapy alone. These trials and their clinical findings were possible only because of the nation's investment, through the NCI, in a national clinical trials network.

Source: NCI Cancer Therapy Evaluation Program

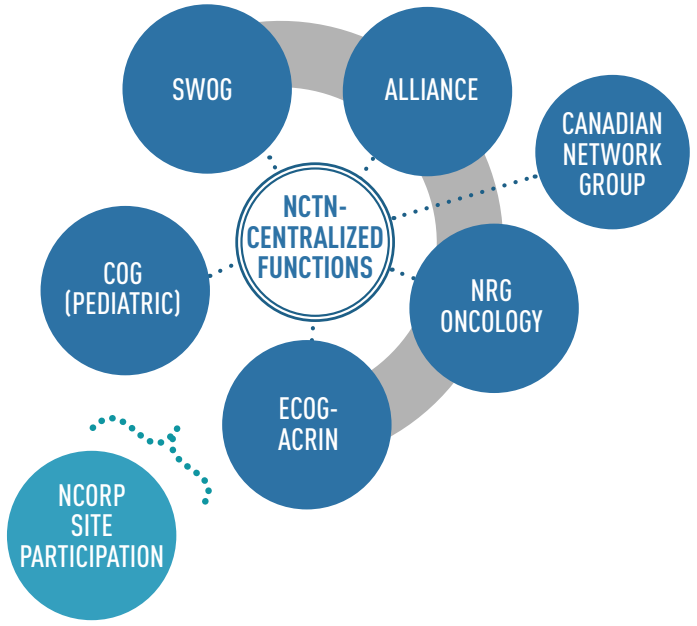
Conducting a new generation of clinical trials requires sophisticated and expensive technologies and clinical processes, including carefully annotated tissue collection, advanced DNA and RNA sequencing methods, and complex analytic algorithms to distinguish normal genetic variants from tumor-specific changes. These, in turn, entail new expenses for surgery, interventional radiology, molecular pathology, and

bioinformatics that have not typically been a part of most clinical trials. In response to recommendations made in an Institute of Medicine report requested by the NCI, the national clinical trials enterprise has been transformed, building on the success of the NCI's Clinical Trials Cooperative Group Program to create a system that can respond more rapidly to scientific opportunities, particularly in conducting genomically based clinical trials. The NCI is now providing a higher percentage of cost reimbursement to the physicians who are treating participants enrolled in clinical trials. Flat budgets, together with the increased cost of conducting state-of-the-art trials, are making it necessary to decrease the number of people participating in clinical trials, which will slow our rate of progress. Many of the new trials now planned through the NCTN depend on new drugs, genetically based diagnostics, and immunotherapies, which have great promise for patients with cancer and are direct outgrowths of the NCI's commitment to basic and early translational science. Some specific trials that are evaluating targeted treatments are described in the section titled *Building on Discoveries in Cancer Genomics*.

This new clinical trials enterprise is a national resource. Although the NCTN is designed to carry out all aspects of advanced clinical trials, the NCI is unable to fully support the network and must rely on the partnership of the institutions and others involved in

NATIONAL CANCER INSTITUTE
National Clinical Trials Network

The National Clinical Trials Network (NCTN) has four U.S. adult cooperative groups (Alliance, ECOG-ACRIN, NRG Oncology, and SWOG) and one pediatric cooperative group (COG). The NCTN also includes a Canadian Network Group because the NCI has had long-standing collaborations with Canadian investigators in clinical trials. Sites that are part of the NCI Community Oncology Research Program (NCORP) can also participate in NCTN clinical trials.



Centralized Functions:
- Centralized Institutional Review Board
- Cancer Trials Support Unit
- Imaging and Radiation Oncology Core (IROC) Group
- Common Data Management System Central Hosting

30 Lead Academic Participating Sites (LAPS)

www.cancer.gov/clinicaltrials/nctn

NCI's National Clinical Trials Network enrolled between 19,000 and 20,000 patients in clinical trials in 2014. Informed consent is an important part of the enrollment process.

the network to cover some costs. For example, a large number of biotechnology and pharmaceutical companies are collaborating with the NCTN on a series of precision medicine trials for some types of lung cancer and other tumor types. Although these partnerships are highly effective and appropriate for some trials, there are some clinical questions for which there are no obvious partners. It is the NCI's responsibility to pursue these trials, especially in the case of rare cancers, but funding levels remain problematic.

In addition, the institute recently launched the NCI Community Oncology Research Program (NCORP). This community-based initiative builds on the scope and activities of the NCI's previously supported community networks—the NCI Community Clinical Oncology Program, the NCI Minority-Based Community Clinical Oncology Program, and the NCI Community Cancer Centers Program—to bring clinical trials, as well as cancer care delivery research, to people in their own communities. This effort enhances patient and provider access throughout the country to clinical trials in prevention, screening, diagnosis, and treatment. It also facilitates the participation of minority and underserved populations in clinical research and accelerates knowledge transfer into clinical practice and health care systems and organizations. Cancer care delivery research is conducted to improve outcomes for patients by translating approaches developed in controlled clinical trials to the community

NCI'S COMMUNITY ONCOLOGY PROGRAMS
IN THE PAST HAVE CONTRIBUTED APPROXIMATELY

25%

OF THE PATIENTS ENROLLED IN
NCI COOPERATIVE GROUP TREATMENT TRIALS

Source: NCI Division of Cancer Prevention

setting and measuring the success of these efforts. The NCORP provides an important connection to community-based cancer care, ensuring that people have access to the benefits of the latest research regardless of where they live. This is a foundational tenet of the NCI.

The **NCORP** provides an important connection to community-based cancer care, **ensuring that people have access to the benefits of the latest research** regardless of where they live.

Overcoming Cancer Health Disparities

As with many diseases, cancer affects some racial and ethnic groups more than others. In addition, because cancer is a constellation of diseases, a given group may be more susceptible to some cancers but not to others. Access to health care may also be associated with the stage at which cancer is diagnosed and, often, with its outcome.

The NCI Center to Reduce Cancer Health Disparities (CRCHD) is a major component of the institute's efforts to overcome the unequal burdens of cancer in our society. The CRCHD (and all of the NCI) supports research to understand the biological differences of cancer among different ethnic and racial groups; identify and overcome barriers to equitable health care; and develop effective, culturally appropriate interventions. Cancer health disparities also represent a major focus of the NCORP. In addition, NCI-supported researchers are evaluating the potential of patient navigation to increase cancer screening rates, improve appropriate follow-up care, and enhance cancer outcomes.

The NCI also monitors trends in incidence and mortality from cancer by race and ethnicity. One notable disparity is a higher overall incidence of cancer among black men (601 per 100,000 men) compared with white men (532 per 100,000 men). Black men also have a higher mortality rate (269 versus 210 per 100,000 men, respectively). Several cancers contribute to these disparities,

The **NCI Center to Reduce Cancer Health Disparities (CRCHD)** is a major component of the institute's efforts **to overcome the unequal burdens of cancer** in our society.

including cancers of the lung, colon/rectum, prostate, stomach, and liver. The NCI supports a range of relevant research, from genomic studies of cancer in black men, to efforts to reduce their tobacco consumption, to evaluating and improving decision making when faced with a lung cancer or prostate cancer diagnosis. Improvements have been seen in reducing the disparities in mortality for some of these cancers. For example, from 2001 through 2010, the mortality rates for lung and prostate cancers among black men fell by 3.3 percent and 3.8 percent per year, respectively. In comparison, during the same time period, the lung cancer mortality rate among white men fell by 2.4 percent per year and the prostate cancer mortality rate fell by 3.3 percent per year.

Another important disparity is seen with breast cancer among black women. Although the overall incidence of breast cancer among black women (123 per 100,000 women) is lower than that for white women (128 per 100,000 women), the mortality rate for breast cancer is higher for black women (31 versus 22 per 100,000 women, respectively). Some of this difference can be attributed to the fact that black women are more likely to have subtypes of breast cancer for which treatment is less effective. One such subtype, triple-negative breast cancer, tests negative for the estrogen and progesterone receptors, as well as for overexpression of the HER2 oncoprotein. Overall, compared with white women, black women are also screened less frequently for breast cancer, are more likely to have advanced disease when a diagnosis is made, have a poorer prognosis for a given stage of disease, and

Michael Jackson is a teacher…and a survivor of prostate cancer. He delayed seeing a doctor before being diagnosed. Michael is now outspoken with his peers about putting their health first. See his story in the "Patient Voices" video series on NCI's YouTube channel, www.youtube.com/ncigov.

have less access to medical care. The NCI supports many kinds of research on breast cancer among black women, including epidemiologic studies examining the role of obesity and other risk factors, basic science studies of genomics and molecular mechanisms, and studies of treatment access and outcomes. The mortality rates for breast cancer have been falling for both black and white women, but the rate of decline from 2001 through 2010 was slower for black women (1.6 percent per year) than for white women (2.0 percent per year).

Improvements in cancer mortality rates have been even slower for American Indians and Alaska Natives. While overall cancer mortality rates from 2001 through 2010 decreased by 1.4 percent per year among whites and by 2.1 percent per year among blacks, they decreased by only 0.7 percent per year among American Indians and Alaska Natives. Among those cancers for which population-wide screening is recommended—cervix, breast, and colon/rectum—American Indians and Alaska Natives are screened less frequently, and the improvements in their mortality rates for these cancers have been smaller than those among whites or blacks. The NCI supports research for American Indians and Alaska Natives to encourage greater use of cancer screening, introduce culturally tailored programs to reduce tobacco consumption, and improve treatment and outcomes from cancer for this population.

The NCI is also working to increase the proportion of underrepresented minorities in the cancer research workforce. For example, the Partnerships to Advance Cancer Health Equity (PACHE) program enables institutions that serve communities with cancer health disparities, including NCI-Designated Cancer Centers, to train scientists from diverse backgrounds in cancer research and the delivery of cancer care to racially and ethnically diverse communities.

The NCI is also working to **increase** the proportion of underrepresented **minorities in the cancer research workforce.**

NCI's Intramural Research Program

Some of the NCI's budget supports the research of scientists who work at the NIH Clinical Center and in offices and laboratories located in Bethesda, Rockville, and Frederick, Maryland. These intramural investigators conduct basic, clinical, and population-based research, including the study of rare cancers, and are encouraged to explore the translation of relevant findings from the laboratory to the clinic. At the NIH Clinical Center, the largest clinical research hospital in the world, intramural researchers are able to quickly test new approaches to cancer prevention and treatment. Clinical studies can be developed in close collaboration with researchers from extramural institutions and the findings extended by extramural investigators. The ability of the NIH Clinical Center to treat patients from all over the world facilitates expeditious clinical research on rare cancers, which may help patients with these diseases and produce insights relevant to more common cancers.

For example, the use of immunotoxins that target a protein expressed in mesotheliomas has produced long-term responses in patients with this relatively uncommon cancer and is leading to clinical trials of this approach in patients with more common tumors. In another, recent advance, adult patients with a type of cancer known as Burkitt lymphoma had excellent long-term

Intramural researchers are able to quickly test their new approaches to cancer prevention and treatment at the NIH Clinical Center, the largest clinical research hospital in the world. Photo of the Mark O. Hatfield Clinical Research Center.

survival rates—upwards of 90 percent—following treatment with low-intensity chemotherapy regimens. Standard treatment for Burkitt lymphoma involves high-dose chemotherapy, which is highly toxic and, historically, cures only 60 percent of adult patients.

The NIH Clinical Center does not come without expense. The NCI and the other NIH institutes and centers support, financially and professionally, the operations of the clinical center, with the NCI covering more of the costs than any other institute.

The intramural program also conducts population and multidisciplinary research to discover genetic and environmental determinants of cancer and new approaches to cancer prevention. Over the years, research by this group of epidemiologists, geneticists, and biostatisticians has influenced public health policy in the United States and around the world. NCI researchers, together with colleagues at the National Institute for Occupational Safety and Health, recently completed the first study to show that heavy exposure to diesel exhaust among miners was associated with an increased risk of developing and dying from lung cancer, even after adjusting for other lung cancer risk factors, such as cigarette smoking. The findings, which took years to develop, played a pivotal role in the recent classification of diesel engine exhaust as carcinogenic to humans (a group 1 carcinogen) by the International Agency for Research on Cancer. The conclusions have implications not just for miners but also for the 12 million American workers and tens of millions more worldwide who are exposed to diesel exhaust in the workplace and for people who live in cities with high levels of diesel exhaust.

Melinda Merchant, M.D., Ph.D., of the NCI Pediatric Oncology Branch, and Ewen Raballand navigate the hallways of the NIH Clinical Center, where Ewen participated in a clinical trial testing natural killer cells to treat his osteosarcoma.
Photo by Daniel Sone

The activities of the NCI intramural research program complement those of other aspects of the National Cancer Program. With both academic and private sector partners, intramural researchers can undertake longer-term projects that may be difficult, if not impossible, through traditional funding mechanisms. For example, NCI researchers studied immunotherapy during long periods when it was not in vogue.

Researchers Bruce Shapiro, Ph.D. (left), and Kirill Afonin, Ph.D., of the NCI intramural program's Basic Research Laboratory study RNA structure, RNA folding, and RNA nanobiology.
Photo by Rhoda Baer

However, the findings from this long-term research made important contributions to the current widespread efforts to develop immunotherapy as a standard of care for a range of cancers. In addition, some public health issues, as exemplified by the diesel exhaust study, take many years and would be very difficult to conduct without government support.

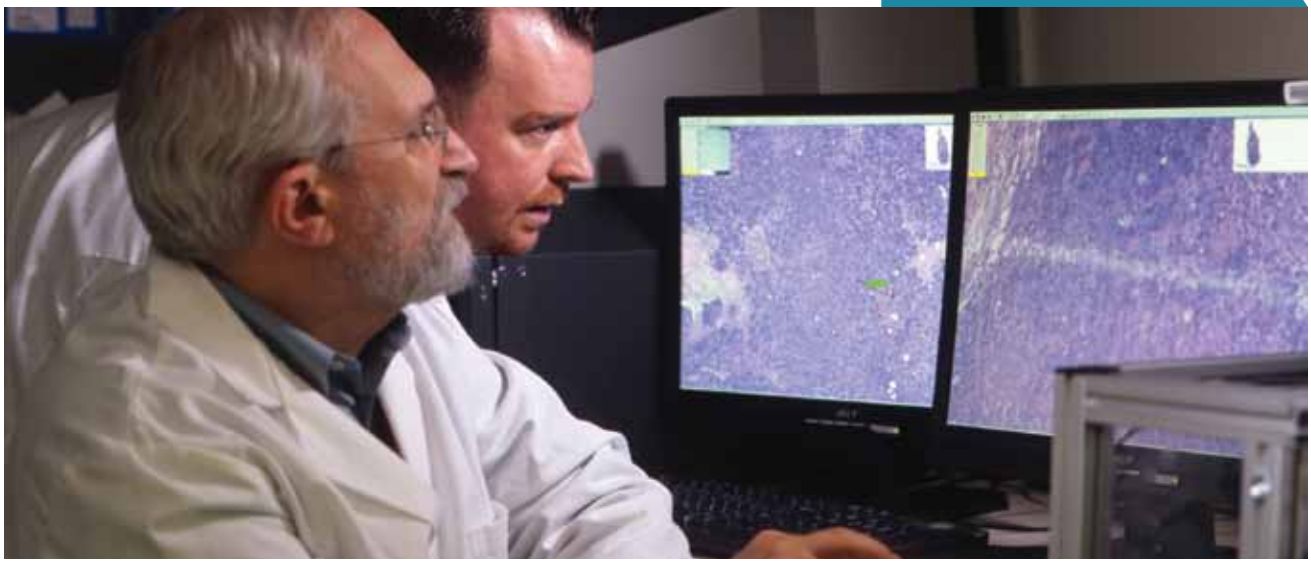
Bioinformatics to Accelerate Research

Bioinformatics, which enables the management and use of very large sets of molecular and clinical data, has become a core component of the NCI's research enterprise. The National Cancer Informatics Program (NCIP), part of the NCI Center for Biomedical Informatics and Information Technology (CBIIT), is the institute's main bioinformatics initiative. The collection, analysis, storage, retrieval, and distribution of "big data" are essential for many aspects of cancer research—especially for cancer genomics, in which millions of data points are frequently collected on each patient—and the monitoring of clinical trials.

The NCI's efforts in this area include ensuring the availability and usability of cancer research data to the broader cancer community. For example, a new study details how a suite of web-based tools provides the research community with greatly improved capacity to interrogate data derived from large collections of genomic information against thousands of drugs. By comparing drugs and genetic targets, researchers can begin

to identify pharmaceuticals that may be effective against different forms of cancer. In addition to furthering research itself, this information may be used in patient diagnosis and treatment. Part of the current effort involves the use of "cloud computing" to manage the vast amounts (about 20 petabytes; 1 petabyte = 10^{15} bytes = 1 million gigabytes) of genomic data generated by TCGA for adult tumors and the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative for pediatric tumors, and to assemble and, ultimately, integrate clinical data in manageable forms. Researchers anticipate that, in the near future, genomic analyses of tens of thousands of cancers will be shared with the research community. Keeping up with the pace of acquisition of new information and ensuring that it remains retrievable in useful ways for basic researchers and clinical investigators requires continual upgrading of the bioinformatics infrastructure, systems, and software, which is critically important and expensive.

Keeping up with the pace of acquisition of new information...**requires continual upgrading of the bioinformatics infrastructure**, systems, and software, which is critically important and expensive.



Paul Meltzer, M.D., Ph.D. (foreground), directs the NCI Clinical Molecular Profiling Core, which facilitates the collection of biological data on tumors.
Photo by Rhoda Baer

The Frederick National Laboratory for Cancer Research provides its researchers with scientific tools, services, and information to enable and expedite their investigations.

Frederick National Laboratory for Cancer Research

The only Federally Funded Research and Development Center (FFRDC) dedicated to biomedical research was established in 1971 under the National Cancer Act. This national resource, overseen by the NCI, provides rapid response capabilities and one-of-a-kind resources for the entire biomedical research community. Its scientists develop technologies and perform studies to support the NCI's mission, as well as the work of other NIH institutes. Like Los Alamos, Brookhaven, Sandia Labs, and others, this FFRDC uses a unique contract mechanism to bring public and private partners together to solve difficult medical research challenges.

A key component of this FFRDC is running the Frederick National Laboratory for Cancer Research (FNLCR). As part of its ongoing commitment to cancer researchers, the FNLCR provides scientific tools, services, and information to enable and expedite their investigations. These include:

- The Biopharmaceutical Development Program (BDP) — This program produces novel antibodies and other proteins that require early development or are not ready for industry to take on. For example, when the Children's Oncology Group wanted to test the therapeutic value of ch 14.18, a monoclonal antibody directed against the protein GD2, which is expressed on the surface of neuroblastoma tumor cells in children, the BDP produced the antibody for the clinical trial because there was no commercial producer. The findings of the trial indicated that ch 14.18 helped to reduce the risk of recurrence when given to children whose disease had responded favorably to standard chemotherapy. The monoclonal antibody, which the

BDP has continued to produce as needed, has now become the standard of care for children with this type of neuroblastoma. Its production is being transferred to the pharmaceutical company United Therapeutics.

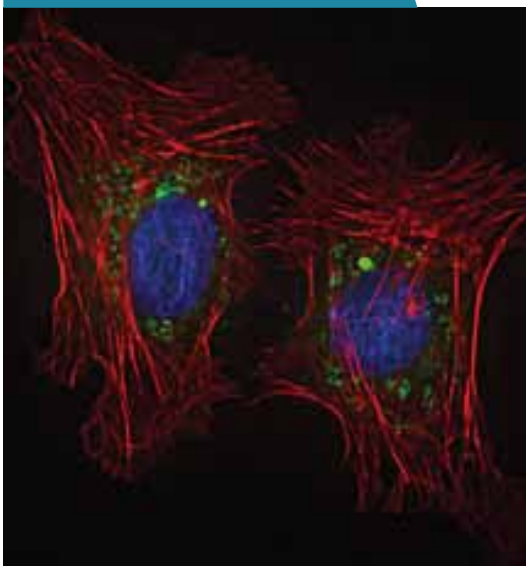
- The Nanotechnology Characterization Laboratory (NCL) — This lab is part of the NCI's Alliance for Nanotechnology in Cancer initiative, which is accelerating the development of nanotechnology for basic and applied cancer research. The NCL, which works together with the FDA and the National Institute of Standards and Technology (NIST), performs and standardizes the preclinical characterization of nanomaterials intended for cancer therapeutics and diagnostics developed by researchers from academia, government, and industry. By providing critical infrastructure and characterization services to nanomaterial providers, the NCL accelerates the transition of basic nanoscale particles and devices into clinical applications. The NCL has evaluated more than 200 nanoparticle formulations, many of which have gone forward into clinical testing. The lab has also helped to establish widely adopted standards for nanoparticles and contributes directly to the education of the next generation of nanotechnologists through biotechnology training courses in nanomedicine and an NCL–NIST postdoctoral training program in chemistry.

- NCI's Experimental Therapeutics (NExT) program — NExT advances breakthrough discoveries in basic and clinical research into new therapies to treat patients with cancer by safely shortening the timeline for new drug development. The program consolidates the NCI's anticancer drug discovery and development resources in support of a balanced therapeutics pipeline, from the validation of new targets to evaluation in phase III clinical trials. For example, promising molecules, such as cediranib (AZD2171), an angiogenesis inhibitor, and olaparib (AZD2281), which inhibits the repair of DNA damage, are being used in combination to treat ovarian cancer and mesothelioma in clinical trials. Another promising therapeutic, selumetinib (AZD6244), which inhibits the activity of an enzyme called MEK in an important cancer growth pathway, is being developed to treat childhood brain tumors.

- The RAS Initiative — This effort was initiated to develop effective therapies against tumors that contain mutations in members of the *RAS* family of oncogenes. The initiative is discussed in the section titled *Developing Therapies for* RAS*-Driven Cancers.*

Photograph of two cells that have taken up drug-bearing polyethylene glycol-coated nanoparticles (green). Inside the cells, the nanoparticles will degrade, releasing their drug payload. The cells' skeletons are stained red, and the cells' nuclei are stained blue.

Photo by Omid Farokhzad, M.D.



Today's progress in cancer research creates opportunities to bring new approaches to cancer prevention, diagnosis, and treatment tomorrow.

Thanks to investments made in understanding the interactions between genes and the environment and the changes that lead to cancer, we are poised to offer strategies for preventing and treating cancer that are tailored to these changes. Precision medicine offers the promise of being able to decrease the risks of disease and optimize treatment for individuals based on understanding the specific causes of cancer as well as the genomic profiles of cancer. The outcome of this research has the potential to prevent more cancers in the first place and, for those who receive a diagnosis, enable them to live longer lives. However, the current cost of research is substantially higher than it was even a decade ago, and maintaining the pace of this progress requires increased support.

Building on Discoveries in Cancer Genomics

Scientists recognized that it would be necessary to decipher the genomes of many cancers to understand the extent of their complexity and diversity. This understanding led the NCI to launch two large research programs that have undertaken the comprehensive analysis of the DNA and RNA in approximately 10,000 tumors from more than 30 types of cancer. These programs are TCGA for adult tumors and TARGET for childhood cancers.

TCGA is a joint project of the NCI and the NHGRI. This comprehensive program, made possible by advances in sequencing technologies beyond those used to sequence the human genome, has resulted in substantial progress in understanding the biology of cancer and has led to new approaches to cancer diagnosis and treatment.

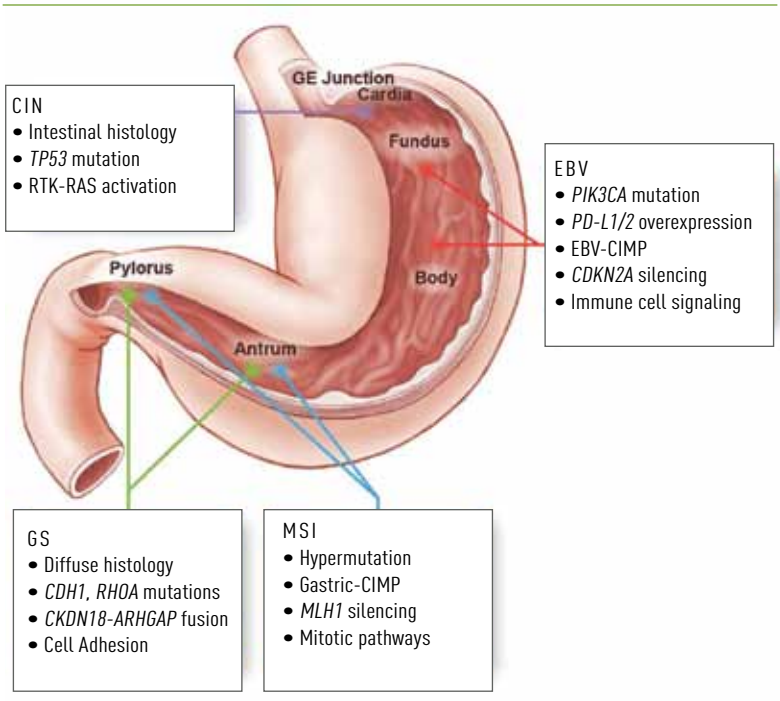
TARGET is a TCGA-like effort in children's cancers that is managed by the NCI. Genomic technologies are being used to search for therapeutic targets in five cancers that are common in, but not always exclusive among, children: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), neuroblastoma, osteosarcoma, and high-risk Wilms tumor.

Technical advances in DNA and RNA sequencing have resulted in substantial progress in understanding the biology of cancer. A technician operates a DNA sequencing machine.

Photo by the National Human Genome Research Institute

TCGA and TARGET have brought together several hundred investigators to work on various cancer projects, which also required the development of an efficient infrastructure for organizing the many steps involved in processing and sequencing the DNA in each tumor and storing the large amount of generated data in a readily retrievable format for analysis. The technical resources, reagents, and personnel for these programs represent a considerable investment by the NCI and the NHGRI. Support for these large, ambitious programs was greatly facilitated by the increased funding associated with ARRA, which led to faster progress in completing the analyses of the various tumors. To build on this momentum, the extensive information developed by TCGA and TARGET is stored in databanks that can be accessed and analyzed by the entire cancer research community, even before papers arising from the data have been published.

Analysis of the tumors in TCGA and TARGET has made it possible to organize each tumor type, often for the first time, into subsets that share particular genetic and epigenetic changes. The latter type of changes, unlike genetic changes, are potentially reversible, which makes it possible to consider treatment to re-express epigenetically silenced genes in the tumor or to silence genes that have been aberrantly activated epigenetically. The targeting of some of the identified genetic abnormalities can be evaluated by using drugs that have already been approved by



Source: Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; 513 [7517]: 202-209.

TCGA analysis of stomach tumors identified Epstein-Barr virus (EBV) as the probable cause of a distinct subset of stomach cancers and suggested new approaches for its treatment. This illustration lists some of the features associated with each of the four molecular subtypes of gastric cancer.

the FDA or experimental drugs that are in clinical trials. In addition, there are efforts to develop specific inhibitors to target other identified abnormalities, once they have been validated as key drivers of the tumor types in which they are found.

In one example, TCGA investigators reported that many squamous cell lung cancers have abnormalities in enzymes called protein kinases for which experimental drugs are in development. This finding has led the NCI to develop the Lung-MAP trial, a master protocol for patients with this form of lung cancer, who will receive experimental targeted treatments as determined by the molecular abnormalities present in their tumors.

In another example, TCGA analysis of stomach tumors identified Epstein-Barr virus (EBV) as the probable cause of a distinct subset of stomach cancers and suggested new approaches for its treatment. EBV had been identified previously in some stomach cancers, but the significance of this finding remained uncertain. However, TCGA analysis indicated that a wide range of tumor suppressor genes are epigenetically silenced in EBV-positive stomach cancers and, in addition, that most of the tumors have mutations in a particular protein kinase for which experimental inhibitors are currently in clinical trials. It should therefore be possible to test whether reactivating these silenced tumor suppressor genes and/or inhibiting the mutated protein kinase can help patients with this cancer.

In acute myeloid leukemia, TCGA investigators identified at least one key mutation in every case, a finding with both short- and long-term clinical implications.

In glioblastoma multiforme, an aggressive form of brain cancer, reactivation of the tumor was found to occur through epigenetic changes, an observation with potential implications for preventing reactivation.

Although it is recognized that cancers at a given organ site may have several subtypes, some important characteristics may be shared among cancers that arise at different sites. For example, TCGA researchers identified four genomic-based subtypes of endometrial cancer and, in addition, uncovered important similarities between endometrial, ovarian, and breast cancers.

Recognizing the value of comparing genomic data from diverse types of cancer, TCGA investigators developed a formal project for cross-tumor analysis called the Pan-Cancer project. This effort has brought together more than 250 collaborators from 30 institutions to analyze the same dataset. It is leading to a deeper appreciation of features common to several cancer types. Some of the results point to potential new uses for existing drugs based on shared molecular targets across cancer types.

Recognizing the value of **comparing genomic data from diverse types of cancer,** TCGA investigators developed a formal project for cross-tumor analysis called the **Pan-Cancer project.** This effort has brought together more than 250 collaborators from 30 institutions to analyze the same dataset.

A recent analysis of 12 cancers by TCGA investigators identified 11 major subtypes based on their molecular profiles. Although some types were specific to their organ site of origin, others, such as squamous cell lung, head and neck, and a subset of bladder cancers were found to have many shared molecular characteristics between organ sites. Such analyses are leading to a potentially new classification of tumors according to their molecular abnormalities, which would go beyond the traditional histologic classification according to the site of origin. A molecular classification may have therapeutic implications in addition to highlighting similar pathogenetic features between cancers of different origins. Finding that a particular targeted treatment is beneficial in one form of cancer may indicate that it could also be clinically useful in other tumor types that share similar molecular abnormalities.

Advancing Precision Medicine Trials

The advances in cancer genomics achieved by TCGA, TARGET, and other molecularly oriented cancer research projects are leading to new clinical trials for patients whose tumors will be extensively genomically tested and whose treatment will be based on the identified molecular abnormalities. These include the Lung-MAP, ALCHEMIST, and MATCH trials.

The Lung-MAP trial is evaluating patients with squamous cell lung cancer that does not respond to first-line therapy. The study divides patients into multiple treatment arms based on the molecular profiles of their cancers, uses targeted drugs and standard chemotherapeutic agents from several pharmaceutical companies, and compares these new approaches to standard second-line treatment. Promising results in any arm can lead to testing the drugs in that treatment arm in more patients, with the goal of more rapidly determining whether the new treatment represents a substantial advance over the standard treatment. This trial is a public–private partnership between the NCI, several pharmaceutical companies, the Foundation for NIH, and Friends of Cancer Research.

ALCHEMIST will test the benefits of molecularly targeted adjuvant (post-surgical) treatment of patients with early-stage lung adenocarcinomas whose tumors have either an *EGFR* gene mutation or an anaplastic lymphoma kinase (*ALK*) gene rearrangement. Depending on the genetic abnormality in a tumor, the patient will receive the EGFR protein kinase inhibitor erlotinib (Tarceva) or the ALK protein kinase inhibitor, crizotinib (Xalkori). These molecularly targeted therapies are FDA approved for

Promising results in any arm [of the Lung-MAP trial] can lead to testing the drugs in that treatment arm in more patients, with the goal of **more rapidly determining whether the new treatment represents a substantial advance** over the standard treatment.

advanced lung adenocarcinoma in patients with the relevant genetic changes. The trial will test whether treating patients earlier in the course of the disease may give even better results. If patients develop resistance to these drugs, as eventually happens with most advanced tumors, the resistant tumors will be biopsied to identify the causes of resistance and to see whether, in future trials, the resistance might potentially be overcome or prevented by alternative treatment approaches. It is expected that most patients with early lung adenocarcinoma who are screened will not be eligible for the therapeutic portion of this trial because their tumors will not have the necessary mutations. However, the tumor samples from these patients will be saved, and, if they relapse while on standard treatment, their tumors will be biopsied again and analyzed for insight into the progression of their disease and for potential therapeutic approaches suggested by this analysis.

Researcher preparing tissue specimens for molecular analysis.

Photo from the NCI Biorepositories and Biospecimen Research Branch

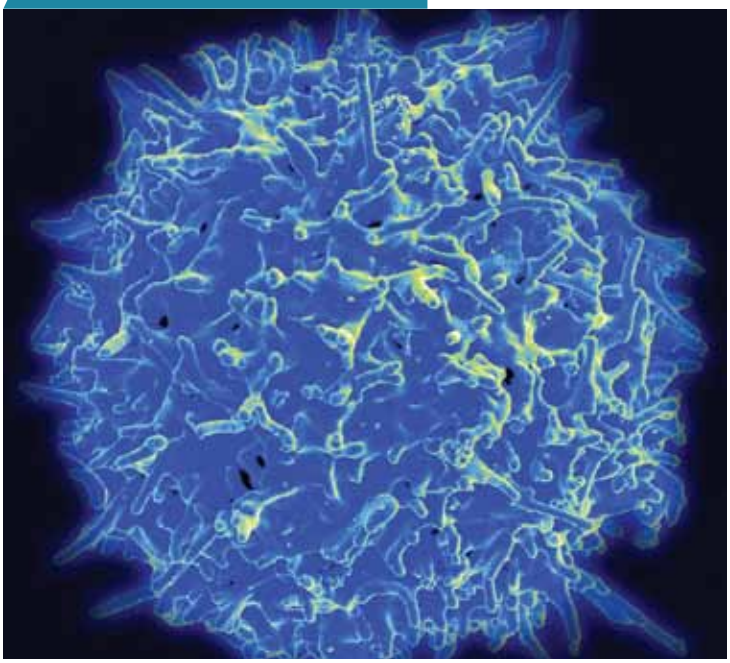
Although most trials study cancers arising at a particular anatomic site, the MATCH trial changes this paradigm by emphasizing the molecular abnormality and by testing a large number of chemotherapeutic agents in virtually any tumor type in which appropriate abnormalities are identified. This umbrella protocol will examine between 20 and 25 drugs, including those that have been FDA-approved for the treatment of cancer at another tumor site or experimental agents that have shown activity against a known target at one or more tumor sites. If the response rate to a particular agent is high, the number of patients evaluated with that treatment will be expanded to further explore whether the targeted treatment represents a substantial advance over standard chemotherapy. If a tumor becomes resistant to the first test drug, it will be re-biopsied to see if another targeted therapy might be effective and to understand the basis for resistance to the initial treatment. By studying multiple agents at the same time, a higher proportion of patients will be eligible for the trial, and efficient progress can be made in the assessment of clinical benefit.

Harnessing the Promise of Immunotherapy

In contrast to therapeutic approaches that target the abnormalities in cancer cells with small-molecule inhibitors, an alternative successful approach is to harness the potential of the immune system to seek and destroy cancers. Therapeutic monoclonal antibodies such as trastuzumab (Herceptin) have been in use since the 1990s. However, their function is analogous to that of the small-molecule drugs, in that these antibodies bind to and inhibit cancer cell proteins that drive abnormal growth. In contrast, therapeutic monoclonal antibodies that modulate immune system activity do so by targeting proteins that normally restrict the strength of immune responses. This approach is based on the hypothesis, from fundamental studies of the immune system, that inhibiting one or another of these "checkpoint" proteins should enable the immune system to help destroy a tumor. The clinical validity of this approach has been confirmed: A monoclonal antibody, ipilimumab (Yervoy), that interferes with the activity of one of these proteins, called CTLA4, was approved by the FDA in 2011 for the treatment of advanced melanoma.

This success is now leading to efforts to improve the effectiveness of anti-CTLA4 antibody treatment in melanoma, identify other tumors where this treatment can have clinical value, and test whether interfering with other immune checkpoints may also have clinical benefit. Such antibody-based inhibitors in development include those that target the proteins PD-1 and PD-L1, which binds to PD-1. Clinical responses in several forms of cancer have been reported with antibodies that target either protein. The FDA has given its "breakthrough therapy" designation to several candidate antibodies, which has facilitated their use in clinical trials and led to the recent FDA approval of the first PD-1 inhibitor, pembrolizumab (Keytruda).

Another antibody-based approach involves fusing a specific monoclonal antibody to a bacterial toxin, which creates an "immunotoxin" that selectively



Electron microscope image of a human T lymphocyte. Stimulating the activity of these white blood cells is one focus of immunotherapy.

Image from the National Institute of Allergy and Infectious Diseases

kills cancer cells because the antibody binds to a protein that is highly expressed on the cancer cells but not on normal cells. Immunotoxins developed by NCI researchers have induced remissions in patients with several cancer types, including late-stage mesothelioma, triple-negative breast cancer, hairy cell leukemia, and childhood acute lymphoblastic leukemia. Immunotoxins will soon be tested in lung adenocarcinoma, pancreatic cancer, and ovarian cancer.

Phineas Sandi, shown here on his first day of kindergarten, participated in an NCI clinical trial that tested genetically engineered T cells to treat acute lymphoblastic leukemia. He was in remission within 11 days of starting the trial and remains free of cancer.
Photo from Kristina Sandi

Directly engineering the patient's own immune cells to recognize and attack their cancer is yet another form of immunotherapy. This approach is called chimeric antigen receptor T-lymphocyte adoptive cell transfer. In this therapy, T lymphocytes from the patient's immune system are genetically engineered to express proteins on their cell surfaces

Directly **engineering the patient's own immune cells** to recognize and attack their cancer is [a form of **immunotherapy**] called chimeric antigen receptor T-lymphocyte adoptive cell transfer.

that enable the cells to recognize and destroy cancer cells. Next, the engineered cells are grown in the laboratory to greatly expand their numbers before they are infused into the patient. The expressed proteins are hybrids of a receptor on the outside of the T lymphocytes that can recognize and bind to a protein on the surface of cancer cells and stimulatory molecules. When the receptor binds to the cancer cell, the stimulatory molecules activate the T lymphocytes to multiply and kill cancer cells.

Long-term responses have been obtained using this approach in adult and pediatric patients with various forms of leukemia and lymphoma. The technology for this promising therapy is still cumbersome and expensive. However, it could have the potential for use in a large number of patients, if appropriately automated cell culture systems can be developed.

Therapeutic vaccines that induce clinically beneficial immune responses are an alternate approach. Some target nonmutated proteins expressed by the tumor, while others target mutant proteins in the tumor. An experimental prostate cancer vaccine against a nonmutated protein (prostate-specific antigen, PSA) has produced long-term responses and is in late-phase clinical trials. Targeting mutant proteins, which is often called neo-antigen vaccination (neo = new; antigen = a part of a protein that induces an immune response), has thus far been successful in animals. It has the theoretical appeal of being directed against proteins whose mutations have been identified by genomic analysis of the tumor.

The journal *Science* designated "immunotherapy of cancer" its Breakthrough of the Year in 2013, thanks to the recent progress made in patients. These clinical advances have come from long-term basic research on the immune system and studies in the NCI intramural research program. These efforts validated the hypothesis that this approach could lead to lasting remissions. It is notable that this research was done during a time of considerable skepticism about the clinical value of immunotherapy. We still need to understand what enables this approach to work in some patients but not others through systematic analysis of their immune systems and their tumors. Improved understanding will make it easier to administer this type of treatment to those patients who are most likely to benefit from it. It could also help researchers develop ways to use this approach to help patients for whom it is not yet beneficial.

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Making Progress against Childhood Cancers

The NCI recognizes the importance of research that addresses pediatric cancers and has an extensive research portfolio that is directly or indirectly related to cancers in children. The institute's support ranges from the conduct of basic science to improve our understanding of the mechanism of disease to the testing of new therapies, including those abandoned by industry. Although significant reductions in pediatric cancer death rates continue to occur each year, about 2,000 children still die annually from cancer, and cancer remains the leading cause of death from disease among children.

The TARGET program uses genomic approaches to catalog the full range of molecular changes in several childhood cancers to increase our understanding of their pathogenesis, improve their diagnosis and classification, and identify new candidate molecular targets for better treatments. The related Cancer Genome Characterization Initiative includes genomic studies of various pediatric cancers that often do not respond well to treatment. TARGET has identified many new mutations and chromosomal abnormalities associated with pediatric cancers; these studies have already led to two clinical trials with new drugs against childhood tumors.

The Children's Oncology Group (COG) is part of the NCTN. It develops and coordinates pediatric cancer clinical trials that are available at more than 200 member institutions, including cancer centers throughout the United States and Canada. In addition to

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Karen Kinahan, M.S., R.N., (left), director of the STAR program at Northwestern University's Lurie Comprehensive Cancer Center, which provides long-term care for adult survivors of childhood cancers, and Julia Stepenske, childhood cancer survivor and stem-cell transplant nurse, at an event celebrating the STAR program's 10th anniversary.
Photo from Karen Kinahan

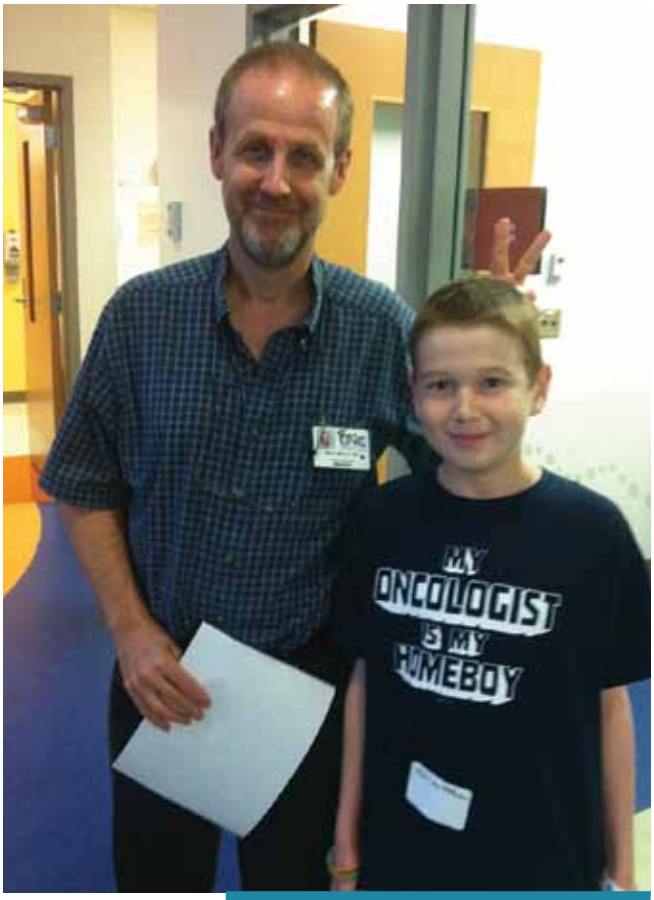
conducting traditional late-phase clinical trials, COG has established its Phase 1 and Pilot Consortium to conduct early-phase trials and pilot studies so that new anticancer agents can be rapidly and efficiently introduced into the pediatric setting. COG will also conduct a new Pediatric Molecular Analysis for Therapy Choice Program (Pediatric MATCH) trial, which will provide opportunities to test molecularly targeted therapies in children with advanced cancers and few other treatment options. This precision medicine trial is modeled on the adult MATCH trial discussed in the section titled *Advancing Precision Medicine Trials*. The Pediatric MATCH trial will enroll children with cancers that have progressed on standard therapy. DNA sequencing of their tumors will be used to identify children whose cancers have a genetic abnormality for which either an approved or investigational targeted therapy exists. Immunotherapeutic approaches will be considered for those children for whom no molecularly appropriate therapy is available.

Childhood cancer survivors are at increased risk of developing secondary cancers and many other long-term health conditions commonly referred to as "late effects" of cancer treatment. The Childhood Cancer Survivor Study (CCSS) evaluates a long-term retrospective cohort with the twin goals of increasing our understanding of these late effects and improving the quality of life for survivors. The CCCS is studying the long-term effects of cancer and cancer therapy in approximately 35,000 survivors of childhood cancer diagnosed between 1970 and 1999 and approximately 8,000 siblings of survivors.

As noted in the section titled *Frederick National Laboratory for Cancer Research,* the NCI has provided strong support for cancer immunotherapy. The FNLCR's manufacturing of the ch 14.18 monoclonal antibody and COG's successful testing of ch 14.18 in children with advanced-stage neuroblastoma are major successes. Moreover, the experimental approach of treating patients with their own T lymphocytes after they have been modified in the laboratory to express chimeric antigen receptors that recognize specific targets on cancer cells is currently being tested in children with several types of cancer. They include B-cell leukemia or lymphoma, synovial sarcoma, osteosarcoma, and other non-neuroblastoma solid tumors.

The NCI supports research to develop treatments specifically for children because children are not just small adults. At the same time, we are actively pursuing drugs that have been effective in treating adult cancers and show promise for certain childhood cancers. To that end, the Pediatric Preclinical Testing Program (PPTP), which identifies new candidate agents for treating childhood cancers, has collaborated with more than 50 companies to undertake the preclinical evaluation of more than 80 therapeutic agents. To date, several PPTP-tested agents have moved into clinical testing.

To take advantage of new information about pediatric cancer, especially in genomics, the NCI plans to convene a workshop in 2015 to discuss the opportunities for future improvement in detection, diagnosis, prevention, and treatment that build on recent genetic discoveries. The workshop participants will include representatives from the pediatric cancer advocacy community, as well as those from philanthropic foundations with an interest in pediatric cancer research.



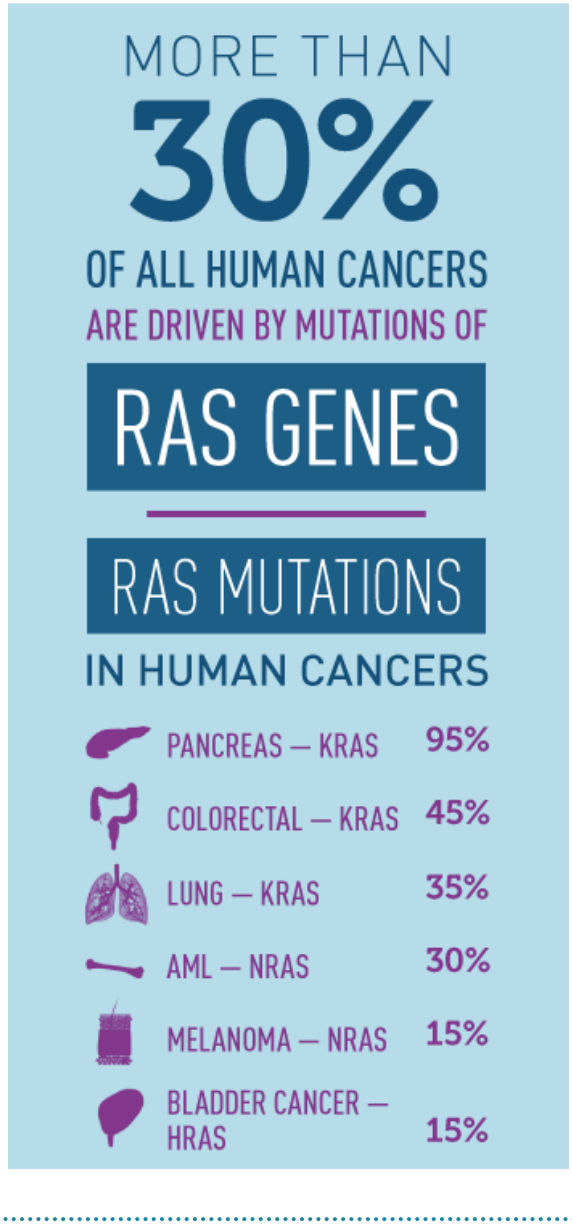
Harrison McKinion (right) was diagnosed with B-cell acute lymphoblastic leukemia in which the genes *EBF1* and *PDGFRB* were rearranged. Brent Weston, M.D., of the UNC Lineberger Comprehensive Cancer Center, reports that Harrison has responded well to imatinib therapy and is expected to complete treatment in the spring of 2015.

Photo from Ginger McKinion

The NCI supports research to develop **treatments specifically for children** because **children are not just small adults.**

Developing Therapies for *RAS*-Driven Cancers

The NCI has recently initiated a project to develop effective therapies against tumors that contain mutations in members of the *RAS* family of oncogenes. Despite advances made with targeted treatments directed against the proteins produced by several other oncogenes that drive cancer, researchers have not yet succeeded in developing effective treatments against proteins produced by *RAS* oncogene family members. It has been known for many years that *RAS* genes are mutated in approximately one-third of all cancers, including the vast majority of pancreatic adenocarcinomas, about 45 percent of colorectal cancers, and about 35 percent of lung adenocarcinomas. As a group, cancers that carry mutations in a *RAS* gene tend to respond poorly to standard chemotherapy and carry with them a poor prognosis. It would therefore be extremely beneficial if there were effective drugs against these cancers. Although there has been considerable progress made in understanding the proteins produced by mutant *RAS* genes, these insights have not been translated into effective drugs, and many properties of these proteins have not been fully explored.



RAS proteins serve as molecular switches that are activated by a specific group of proteins and inactivated by another group of proteins. The majority of mutant RAS proteins are constitutively activated primarily because they are resistant to the proteins that normally inactivate them. RAS proteins appear to lack places where an anticancer compound can bind, leading some investigators to consider these proteins "undruggable." In addition, RAS proteins signal to several downstream targets that together account for *RAS*'s strong cancer-promoting activity. Interfering with just one of these targets does not appear to be clinically useful against tumors driven by mutant *RAS* genes.

However, recent developments, such as improvements in imaging tools and new information about how RAS proteins interact with several other proteins, have suggested that this pessimistic view may not be correct and have fostered renewed interest among researchers in finding ways to target mutant RAS proteins or their signaling pathways with small compounds.

To accelerate progress, the NCI recently launched the RAS Initiative, a large-scale collaborative effort to find vulnerabilities in cancers driven by mutant RAS proteins that may be exploited in efforts to seek therapeutic strategies for patients with *RAS*-driven cancers. This new initiative is based on a "hub and spoke" model, with the Advanced Technology Research Facility of the NCI's FNLCR serving as the initiative's "hub." The project is being led by Frank

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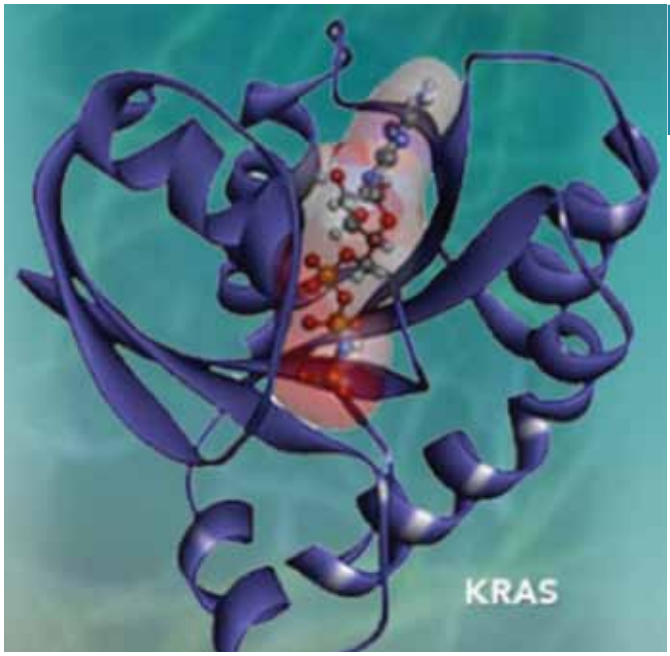

Structure of human KRAS protein.

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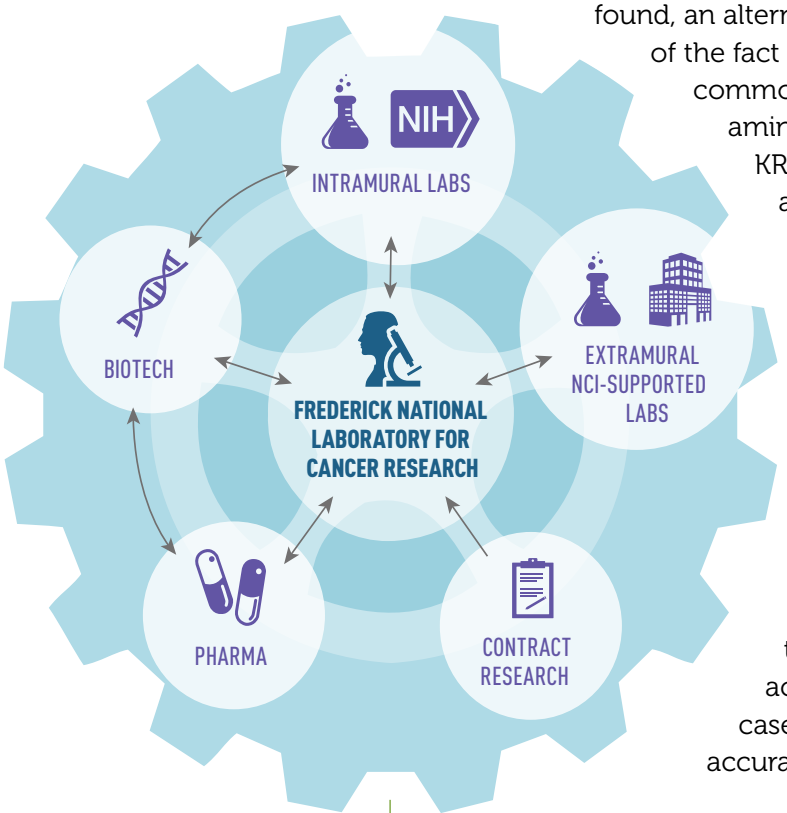
McCormick, a highly respected RAS researcher who, until recently, was director of the NCI-Designated Comprehensive Cancer Center at the University of California, San Francisco. The hub at FNLCR interacts with the "spokes" of academia, the NCI's intramural laboratories, and the biotechnology and pharmaceutical industries. This project highlights the NCI's ability to bring together experts from across the research enterprise to address pressing scientific and clinical questions in cancer.

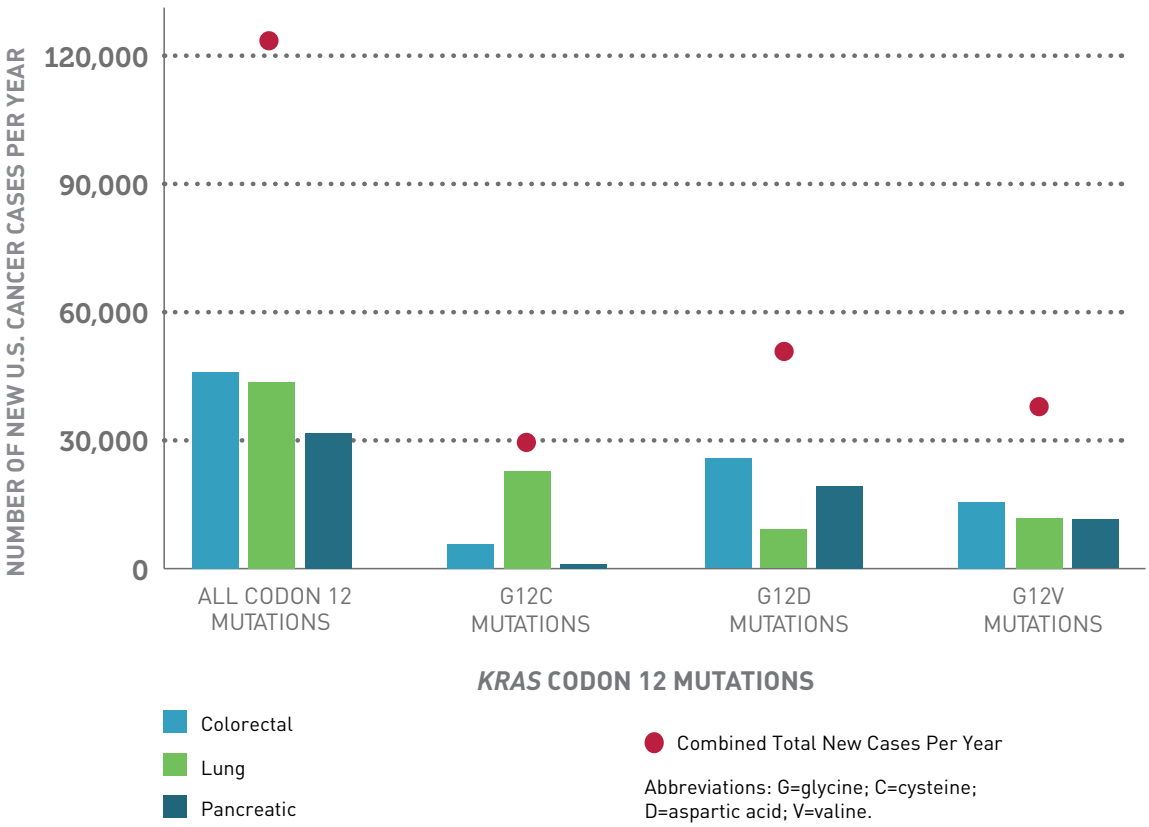


Although it is hoped that a "universal" RAS inhibitor will be found, an alternative approach is to take advantage of the fact that there are several relatively common mutations that change the same amino acid (glycine at position 12) in the KRAS protein to one of three different amino acids (cysteine, aspartic acid, or valine). RAS Initiative researchers will test whether it may be possible to develop inhibitors that work against one or two of these closely related mutant proteins rather than against all mutant RAS proteins. Even this accomplishment could have a substantial impact, because one of these three mutant KRAS proteins is present in more than 100,000 new cancers per year in the United States, with each mutant accounting for more than 29,000 cases. This project will also develop accurate structural models of mutant

RAS proteins and their interacting proteins, an advance that could lead to new approaches for developing drugs that interfere with these interactions. RAS Initiative researchers also plan to identify a range of key genes that cooperate with mutant *RAS* genes to drive cancer cells and to see whether inhibiting them singly or in combination might lead to an effective approach for targeting tumors with mutant RAS proteins. The information developed by the RAS Initiative will be fully available to the research community to further increase the likelihood of progress. In addition, the RAS Initiative is developing a resource of reference reagents for the research community.

INCIDENCE OF *KRAS* CODON 12 MUTATIONS IN THREE HUMAN CANCERS

A codon is a sequence of three nucleotides in a messenger RNA molecule that determines which amino acid will be used during each step of protein synthesis. Codon 12 of *KRAS* messenger RNA normally specifies insertion of the amino acid glycine at postion 12 of the growing KRAS protein molecule, but mutations can cause this amino acid to be replaced with cysteine, aspartic acid, or valine.



Adapted from Stephen AG, Esposito D, Bagni RK, et al. Dragging Ras Back in the Ring. *Cancer Cell* 2014; 25(3):272-281.

Finding New Strategies to Prevent Cancer

Preventing cancer remains a critical goal. Because there may be an interval of several decades from the initial exposure to an environmental carcinogen to the development of cancer, it often takes many years before a decrease in exposure results in a reduction in cancer incidence and mortality. However, a decrease in exposure during this long interval can eventually result in substantial long-term dividends, as seen, for example, with tobacco. The greatest benefit is usually seen if the exposure is eliminated.

Many preventive efforts are directed at reducing or eliminating exposures to carcinogens or protecting the body from exposures. Other efforts may involve screening procedures, such as those for cervical and colorectal cancer, which can find premalignant lesions and lead to treatment of patients who are at high risk of developing cancer. Although the pharmaceutical industry regularly funds diagnostic and therapeutically oriented research, the majority of prevention-oriented research is funded by the public sector because the potential for commercial profit in this area is either substantially less than for treatment or may not exist at all in some instances. Nevertheless, prevention has the potential to save more lives from cancer than treatment—as is already true for tobacco and lung cancer—which underlines the importance of strongly supporting this research area.

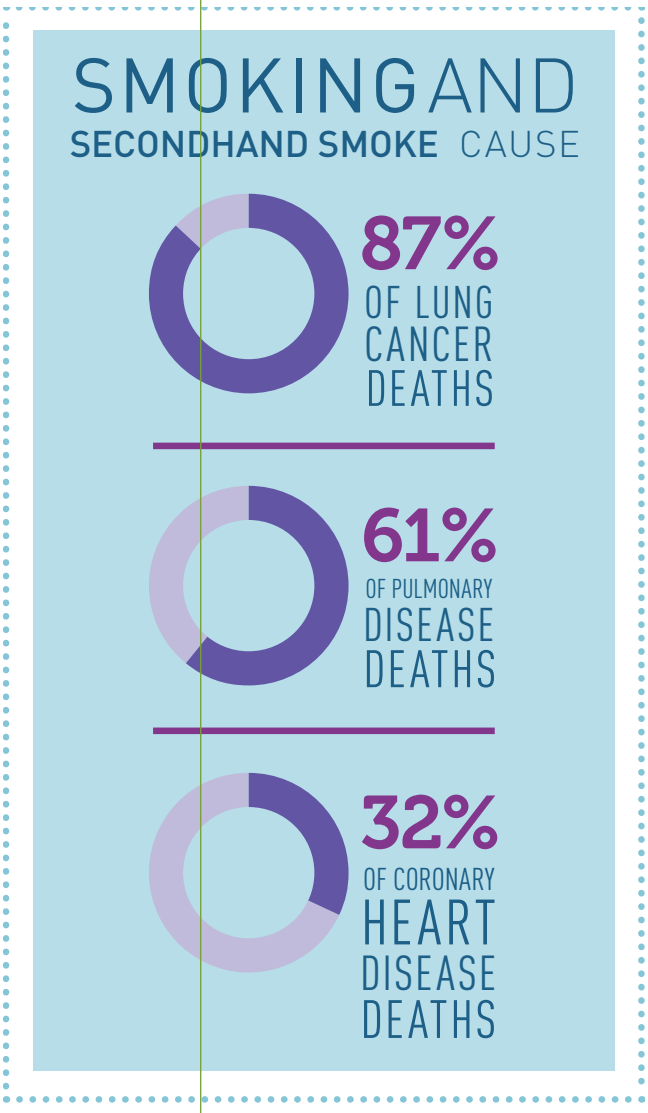
Prevention has the potential to save more lives from cancer than treatment... which underlines the importance of strongly supporting this research area.

As in other areas of research, the cost of prevention research continues to increase, which seriously constrains the kinds of trials that are undertaken. For example, the National Lung Screening Trial (NLST) was started in 2002, during the period of the doubling of NIH funding. When this study of more than 50,000 high-risk current and former smokers was completed

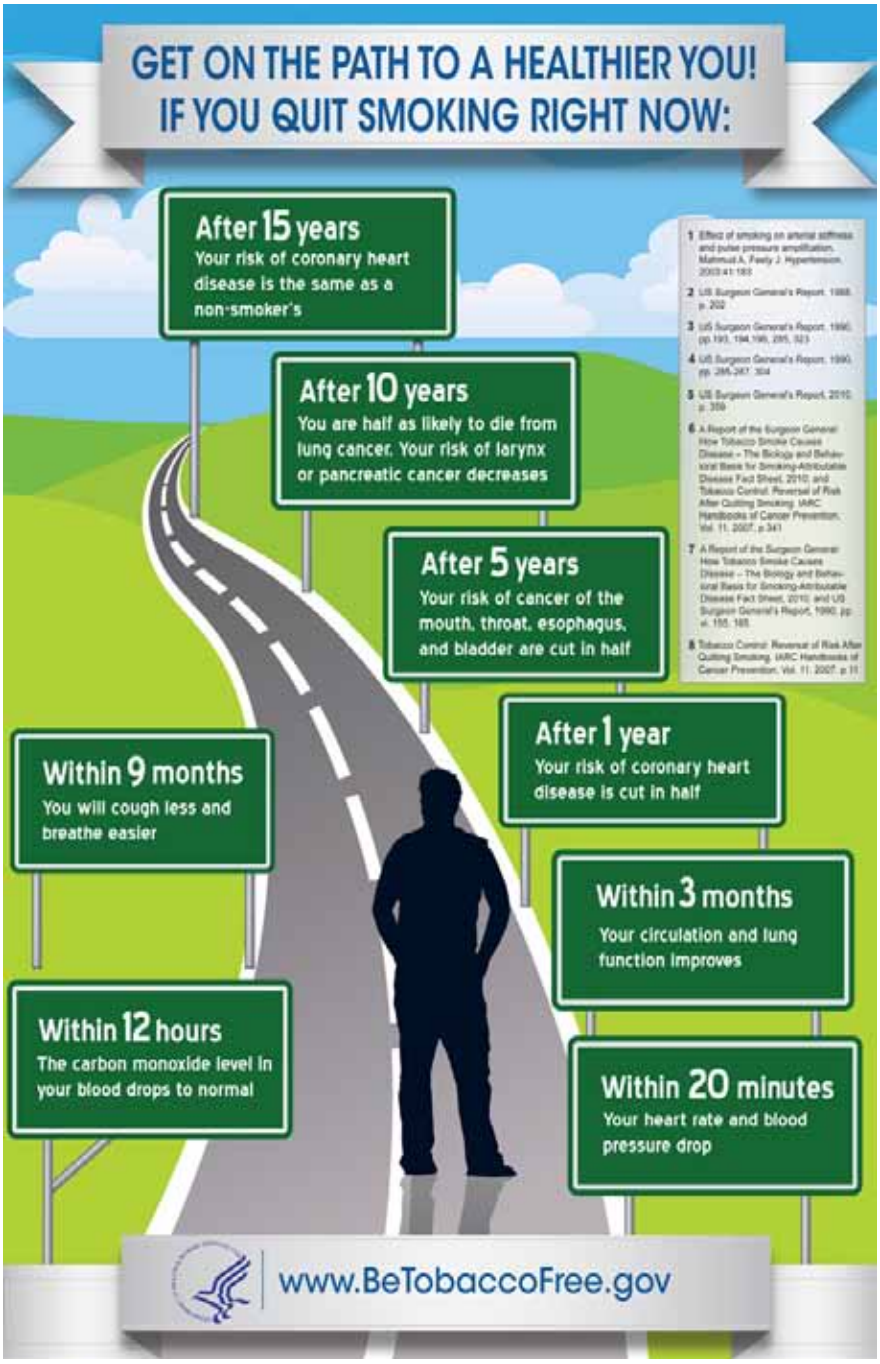
8 years later, it had cost the NCI more than $250 million. However, NLST demonstrated for the first time in a randomized controlled screening trial for lung cancer that a screening approach—low-dose helical computed tomography (CT)—could reduce mortality from lung cancer by almost 20 percent. The findings from NLST have led low-dose helical CT to become the standard of care for screening high-risk current and former smokers. It is not clear whether such a trial, whose potential for success was viewed as very uncertain when it was started, would be initiated in today's funding climate.

Tobacco control. Tobacco use is the single most important known preventable cause of cancer. In addition to being the major cause of cancers in the lung, smoking contributes to cancers elsewhere in the body as well as to cardiovascular and other diseases. It is estimated that the typical smoker in the United States reduces his or her life expectancy by more than 10 years. More than 87 percent of lung cancer deaths, 61 percent of all pulmonary disease deaths, and 32 percent of all deaths from coronary heart disease are attributable to smoking and to exposure from secondhand smoke. If current trends continue, it is estimated that smoking will cause the premature deaths of 5.6 million American youths who are now under the age of 18.

The serious health consequences of tobacco use were highlighted by the landmark 1964 U.S. Surgeon General's Report on smoking and health, which laid the foundation for tobacco control efforts in the United States. Adult smoking rates in the United States declined from 42 percent in 1965 to 18 percent in 2012, preventing serious disease for many Americans. However, more than 42 million Americans still smoke. Epidemiologic research indicates that many of the negative health consequences associated with tobacco consumption are potentially reversible for smokers who quit. For example, compared with someone who continues to smoke, 35- to 44-year-olds who quit can gain about 9 years of life expectancy, 45- to 54-year-olds can gain 6 years, and 55- to 64-year-olds can gain



Source: U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014.



Adapted from BeTobaccoFree.gov

4 years. Ten years after quitting smoking, the risk of death from lung cancer declines by almost one-half, and at 15 years the risk of coronary heart disease is close to that of a person who never smoked.

Other epidemiologic research has found that people in the United States who have more education are less likely to smoke. Although the smoking rate among college graduates is 10 percent, it is 24 percent among high school graduates and 45 percent

among those with a general educational development (GED) certificate. High smoking rates are also associated with low socio-economic status, mental illness, and being Native American. In addition, the states with the highest smoking rates have more than twice the number of adult smokers as those states with the lowest smoking rates. The NCI supports several studies that aim to develop and implement more effective approaches for these groups with high smoking rates to prevent more of them from starting to smoke and to help those who do smoke to stop smoking.

As youth become more attracted to electronic cigarettes, the NCI is addressing this emerging trend and its relationship with tobacco consumption. The NCI recently co-sponsored the NIH Electronic Cigarette Workshop: Developing a Research Agenda. The goal of the meeting was to identify the key research gaps related to electronic cigarettes and their effects on human physiology and health, the potential for addiction to these products, as well as issues related to smoking cessation and other public health concerns. The NCI is using several grant mechanisms, including supplements to the NCI-Designated Cancer Centers, to support research evaluating this nontobacco form of smoking for its potential to increase, or decrease, tobacco consumption, as well as for its possible direct effects on health. We are also working closely with the FDA, which has the major responsibility for regulating tobacco products.

Global tobacco consumption is a serious and growing health problem. The World Health Organization estimates that the number of annual tobacco-related deaths worldwide will increase from almost 6 million today to more than 8 million by 2030, with 80 percent of those deaths occurring in low- and middle-income countries. The NCI and NIH's Fogarty International Center, together with other partners, have launched the International Tobacco and Health Research and Capacity Building Program. This program supports transdisciplinary research and capacity-building projects that address the burden of tobacco consumption in low- and middle-income nations, among many other strategies. The program is designed to promote international cooperation between investigators in the United States and other high-income nations that conduct research on tobacco control with scientists and institutions in countries in which tobacco consumption is an urgent public health concern.

Source: World Health Organization.
WHO Report on the Global Tobacco Epidemic, 2011.

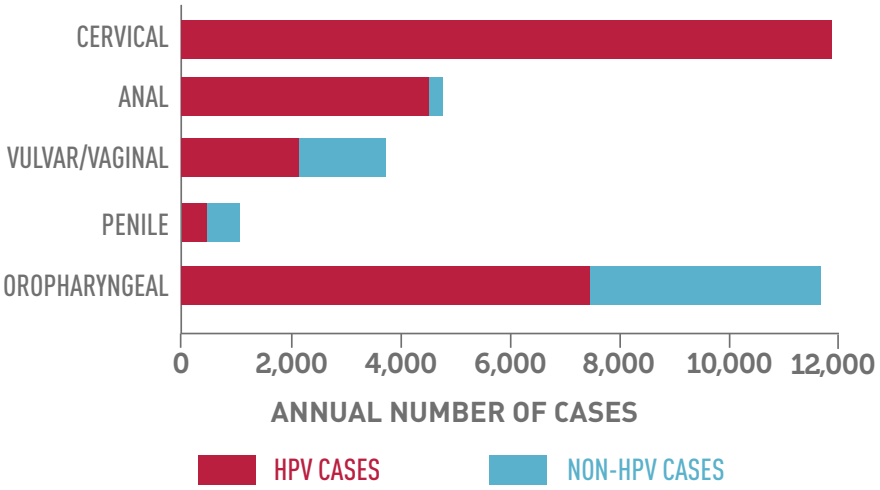
The NCI and NIH's Fogarty International Center, together with other partners, have launched the **International Tobacco and Health Research and Capacity Building Program** [to] address the burden of tobacco consumption **in low- and middle-income nations.**

Preventing cancers caused by viral infections: HPV and HCV. Identifying an infectious agent as a cause of cancer carries with it the possibility of prevention, because we can try to reduce exposure to the agent, develop a vaccine that prevents the infection, or treat the infection before it causes cancer. Identification of hepatitis B virus (HBV) in the 1960s and the recognition that chronic HBV infection is an important cause of serious liver disease, including liver cancer, led to development in the 1980s of the first vaccine that can prevent cancer. Recent developments with two oncogenic viruses, human papillomavirus (HPV) and hepatitis C virus (HCV)—both of which cause cancer after many years of chronic infection—illustrate how a variety of research advances have the potential to substantially reduce cancers attributable to both viruses.

HPV infection causes virtually all cases of cervical cancer and a substantial proportion of several other cancers. In the United States, the number of noncervical cancers attributable to HPV infection is similar to that of cervical cancers. Thanks to decades of Pap smear-based cervical cancer screening and treatment of identified premalignant lesions, there has been an approximately 75 percent reduction in the incidence of and mortality from this cancer since the early 1950s. On the other hand, there have been substantial increases in HPV-associated anal and oropharyngeal cancers, two diseases for which population-based screening has not been determined to be useful. The vast majority of anal cancers are caused by HPV infection, and incidence of and mortality from this cancer increased by 22 percent and 17 percent, respectively, between 2001 and 2010. The incidence of HPV-positive oropharyngeal cancer increased more than threefold during a recent 25-year period, and it is estimated that by 2020 the number of HPV-positive oropharyngeal cancers will be higher than the number of cases of cervical cancer.

PROPORTION OF CANCERS CAUSED BY HPV IN THE UNITED STATES

HPV infection causes virtually all cases of cervical cancer and a substantial proportion of several other cancers.



Source: Schiller JT and Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. *Nat Rev Microbiol* 2012; 10(10): 681-692.

A safe and effective vaccine that, in principle, can prevent most cases of cervical cancer as well as most of the noncervical cancers attributable to HPV infection was approved by the FDA in 2006, followed in 2009 by the approval of a second vaccine. This approach, made possible by earlier work done by NCI researchers, is already having a major impact on reducing the incidence of high-grade cervical dysplasia in young women in Australia, where there has been high vaccine uptake. However, these vaccines are underused in the United States, as well as in low- and middle-income countries, where cervical cancer is frequently the most common cancer among women. As the President's Cancer Panel noted in a recent report, the underuse of HPV vaccines is a serious but correctable threat to progress against cancer. Recent research strongly suggests that two doses, and perhaps even a single dose, of the current vaccines may be sufficient to induce long-term protection in young adolescents. If confirmed to provide long-term protection, reducing the number of doses could make vaccination logistically easier and less expensive. Second generation vaccines with the potential to protect against even more of the HPV-associated cancers are in development.

In 2006, the FDA approved a safe and effective vaccine that can prevent infection with the HPV types that cause most cervical cancers. The underuse of HPV vaccines is a serious but correctable threat to progress against cancer.

The recognition of HPV as a cause of several cancers is also having an impact on research and practice beyond the vaccine, to preventing the cancers after infection. HPV DNA-based testing, which is more sensitive than traditional Pap smear screening for cervical cancer, has been approved by the FDA for use in cervical cancer screening, initially in conjunction with Pap smear screening, and in 2014 as a primary screening method. This approach has the potential to further reduce the incidence of and mortality from this cancer. To reduce the incidence of anal cancer, the NCI has initiated a large screening trial to determine whether treatment of high-grade anal dysplasia identified by screening high-risk patients can reduce their likelihood of developing invasive anal cancer.

HCV infection is a major cause of liver cancer in the United States and throughout the world. Much of the 20-percent increase in liver cancer mortality in the United States seen between 2001 and 2010 is believed to be attributable to this infection. The recognition that HCV is frequently transmitted by blood products led to effective screening methods that have dramatically reduced the incidence of transfusion-related HCV infection. Although efforts to develop a preventive vaccine have thus far been unsuccessful, there has been enormous progress in the development of effective approaches to the antiviral treatment of chronic HCV infection. Several direct-acting antiviral drugs that can induce sustained viral responses have been licensed by the FDA since 2011, and others with potentially promising efficacy profiles are currently in late-phase clinical trials. Long-term follow-up of treated patients will be needed to verify that the treatment has reduced their risk of liver cancer and other serious liver disease. These advances in treatment led the United States Preventive Services Task Force in 2013 to recommend that all individuals born between 1945 and 1965

HPV DNA-based testing...has the potential to further **reduce the incidence and mortality from [cervical] cancer.**

(a group at high-risk of acquiring the virus from contaminated blood products) be screened once for HCV infection. Further research might indicate that it is cost effective to expand the group of individuals who should be screened for HCV infection.

Chemoprevention with aspirin. Evidence from several studies of people who have taken low-dose aspirin for many years shows a substantial reduction in the incidence of and mortality from several types of cancer, including colorectal and lung cancer. However, the adoption of long-term chemoprevention of cancer with aspirin has been limited by concerns about gastrointestinal side effects, such as bleeding, especially in older individuals. The NCI is collaborating with the National Institute on Aging on a 5-year study of aspirin's preventive attributes and side effects in 19,000 people over the age of 65 in the United States and Australia, in hopes of providing information that will better guide the use of aspirin for chemoprevention.

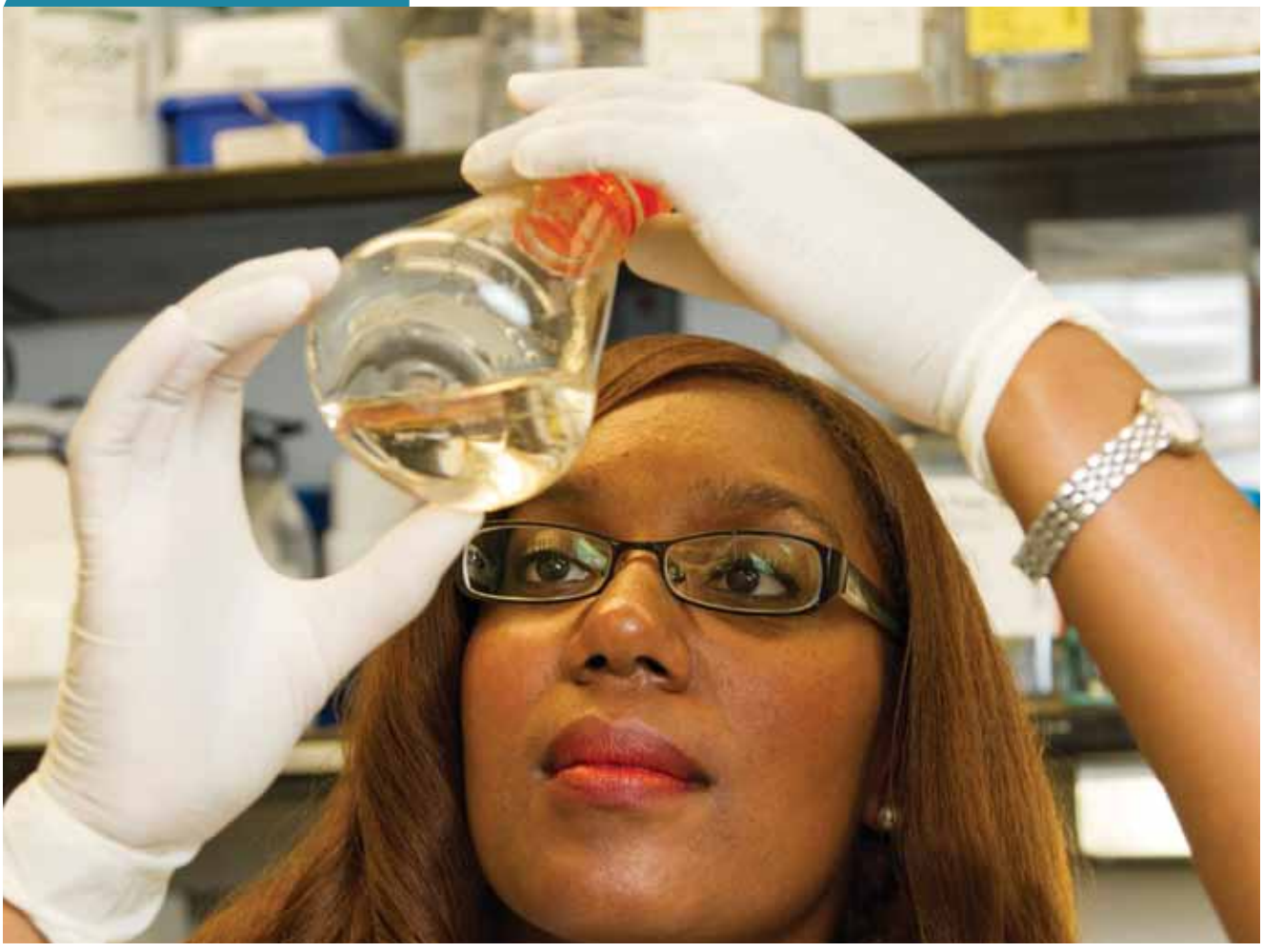
As in cancer treatment, the genomic methods of precision medicine may help to identify patients who are more and less likely to reduce their cancer risk by taking aspirin. A recent retrospective study suggests that some individuals, based on their genetic background, may benefit more than others from the chemopreventive effects of aspirin. In the study, individuals who had higher levels in their normal colon of a particular enzyme in a pathway affected by aspirin and who took aspirin regularly had a 50 percent lower risk of colon cancer than those who did not take aspirin. However, those who had lower levels of the enzyme and took aspirin had only a 10 percent lower risk of colon cancer. Another study reached similar conclusions for the level of a related protein in the urine. If these results are confirmed in other studies, the ability to differentiate between groups who will benefit the most from this approach and those who will not might help doctors and patients make informed decisions about aspirin for cancer prevention.

The Future

The NCI recognizes the need to ensure that the nation's cancer research portfolio supports the continuum from basic to translational to clinical research. As in the past, unexpected basic science discoveries will lead scientists to new areas of cancer research. It also remains important to continue to identify new causes of cancer and to study established causes that we do not fully understand. For example, Merkel cell carcinoma, a relatively uncommon form of skin cancer that is associated with a higher mortality rate than melanoma, was recently found to be associated with infection by Merkel cell polyomavirus (MCPyV). This association has led to a rapid increase in our understanding of the genetics, molecular biology, and pathogenesis of this type of tumor and to new candidate approaches for its treatment.

Chanelle Case Borden, Ph.D., is a post-doctoral fellow in the NCI Experimental Immunology Branch. Investigators like Dr. Borden are the future of cancer research.

Photo by Daniel Sone



In the clinic, it will be critical to continue to identify molecular signatures of subpopulations of tumor types that can be correlated with prognosis or response to drugs. Applying this knowledge for improved screening and diagnosis will help us to better distinguish cancers that are likely to be aggressive from those that are not, leading to the ability to tailor treatment to the disease and provide the patient a better outcome.

The dependence of tumors on the mutation and aberrant expression of particular genes, or on signaling pathways and networks, has led to effective targeted cancer treatments directed at inhibiting these activities. However, the duration of effectiveness is often limited by the development of treatment resistance, which arises from new mutations in the tumor and other mechanisms. The future of cancer treatment with new molecularly targeted drugs will depend on understanding drug resistance, overcoming it, and preventing it through the development of effective combination therapies that address multiple genetic changes over time, as well as alternative treatments that can circumvent resistance.

Thus far, cancer research has identified very few ways to replace the anticancer activities of tumor suppressor genes that are commonly inactivated by mutation or deletion in cancer. Theoretically, such replacements have enormous potential, because we know that most cancers remain susceptible to these genes when nonmutated versions of them are selectively re-expressed. However, the clinical utility of this approach has remained largely elusive because of technical and conceptual barriers. Breakthroughs that can overcome this bottleneck will only come from additional research.

Today's efforts to control cancer and its broad effects—through science, medicine, and social programs—are vast and are conducted by many people in many organizations. The NCI is committed to the continued investigation of the basic biological causes of cancer. Applying that knowledge to develop new prevention, screening, diagnostic, and therapeutic approaches will result in further reductions in cancer incidence and mortality.

> "We need to keep our eye on our own history, and **what has been productive for the NIH has been supporting the most brilliant people to think freely** about solving really difficult problems."
>
> — Harold Varmus, M.D.
> October 21, 2014,
> presentation to the
> NCI Council of Research
> Advocates

Our understanding of cancer is expanding, together with our ability to prevent, diagnose, and treat it.

But, fiscal realities are curtailing the speed at which advances can occur. Despite the NCI's best efforts, too many good ideas are left on the table unfunded. The cancer research community has demonstrated the capacity to utilize additional funds in ways that can accelerate programs and move the increased understanding of cancer into the clinic. TCGA is just one recent example of this capacity. Advances against the worldwide scourge of cancer will depend on strong continued support of the research enterprise and integration of the various modes of research employed by many global partners. This commitment to cancer research will demonstrate the urgency of making progress for current patients and for the many at risk of developing cancer.

They deserve nothing less.

NCI Professional Judgment Budget Recommendation

As the promising research opportunities highlighted in this document demonstrate, the cancer research community—under the leadership of the NCI—is poised to accelerate the rate of discovery and reduce the burden of cancer in America. Achieving these important goals will require resources to support the full continuum of research sponsored by the NCI. Major advances in prevention, diagnosis, and treatment are clearly possible, but they require ample funding across a broad spectrum of science, including basic biological research.

To make rapid progress in cancer research, NCI funding must not only be strong, but also sustained. Yet, recent experience has been discouraging. Measured in inflation-adjusted dollars and excluding any one-time funding, the NCI suffered a 25 percent budget decline due to inflation during the past decade. This decrease represents a cumulative loss of $10 billion in cancer research funding since 2003. As a consequence, the NCI's ability to exploit promising research opportunities and translate these opportunities into new cancer treatments and prevention strategies has been constrained and compromised.

The outlook for funding in the future appears equally discouraging. In the decade ahead, the NCI may experience a repeat of the budget environment that governed the past decade. Based on recent amendments to the Budget Control Act, overall spending on the federal government's discretionary programs—which includes biomedical research—will remain flat through fiscal year 2021, when adjusted for inflation.

If this assessment proves true, and if the NCI budget faces the same constraints as other discretionary programs, then funding for cancer research at the NCI will have suffered nearly 20 years of budget stagnation. During this period, a generation of Americans will grow older, and with their advancing age comes an increased risk of developing cancer. More than 30 million Americans will likely receive a cancer diagnosis during this period, but for too many of these Americans, the research that could have led to better prevention, diagnosis, or treatment of their cancers will not have gone forward or will have advanced at a slower pace than possible, as a result of funding constraints.

The table that follows contains recommended funding increases based on the most promising opportunities identified in this document. Increased funding for these cancer research priorities represents a modest step toward restoring some of the funds that the NCI research budget lost during the fiscal erosion of the past decade.

As a measure of how modest this funding recommendation is, consider the following: If the NCI's annual budget had kept pace with inflation in the cost of biomedical research since fiscal year 2003, NCI cancer research funding would total $6.76 billion for fiscal year 2016. Thus, the $5.75 billion recommended in the table that follows is $1 billion below the amount the NCI would have received if the budget had merely kept pace with inflation. In other words, a budget of $5.75 billion restores only 41 percent of the funding required for the NCI to recover its losses due to inflation.

A budget increase to support the priorities outlined below should not be a solitary event, however. Truly accelerating scientific discovery in ways that can significantly reduce the burden of cancer requires steady annual funding increases for research supported by the NCI. Steady and sustained budget increases will drive progress on preventing, diagnosing, and treating cancer and will measurably improve outcomes for patients with all types of cancer.

Sustained, steady budget increases will also speed progress toward a promising new era of precision medicine, in which the medical community routinely uses detailed genetic information to identify the most effective patient- and tumor-specific approaches to treat cancer. With sustained funding, the NCI can broadly advance and successfully integrate the many disciplines (including genomics, informatics, pharmacology, and cancer biology) required to achieve this era of precision medicine. With sustained investments, the NCI can alter the landscape for the practice of cancer medicine, foster standards for molecular medicine in other domains (such as infectious disease, metabolic disease, cardiovascular disease, and pediatrics), stimulate development of important new therapies within our nation's biomedical industries, and enlarge U.S. prestige for its public health leadership and for improving outcomes for cancer patients across the globe.

National Cancer Institute

FY 2016 Professional Judgment Budget

(dollars in millions)

At a Glance		
Fiscal Year 2015 Estimate	$4,931	
Current Services Increase*	108	
Subtotal	**5,039**	
Fiscal Year 2016 Additional Resources	**Recommended Increase**	**See Details on Page**
Cancer Clinical Trials, including Pediatric Trials	$100	22
Cancer Centers	90	20
Informatics & Computation	50	30
Research Project Grant Pool, including Provocative Questions Initiative & Outstanding Investigator Awards	250	16
Genomics	50	34
Global Health	20	6
Biological & Clinical Research Reagents	30	32
Prevention & Early Detection	50	50
Intramural Research	25	28
Immunotherapy	25	40
Frederick National Laboratory for Cancer Research	25	32
Total Additional Resources	**715**	
Total NCI	**$5,754**	

*The estimated current services inflationary increase is based on the Biomedical Research and Development Price Index (BRDPI) for FY 2015 of 2.2 percent.

View this document online at:

www.cancer.gov/NCIresearchfuture

For more information about the
National Cancer Institute, visit:

www.cancer.gov

Or call the NCI Cancer Information Service:

1-800-4-CANCER

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