NIH NATIONAL CANCER INSTITUTE

# Annual Plan & Budget Proposal

## FOR FISCAL YEAR 2020

U.S. Department of Health & Human Services | National Institutes of Health

# Director's Message: A Time of Great Hope and Great Challenge

As director of the National Cancer Institute (NCI), I am pleased to share our *Annual Plan and Budget Proposal for Fiscal Year 2020*. Having been sworn in to my position a little less than a year ago, this marks my first opportunity to present, in this form, the promising results of our country's investments in biomedical research. This plan directs attention to areas where additional support has unique potential to improve cancer prevention, detection, and treatment.

To place the plan's focus squarely on those most likely to benefit from NCI research, we have included stories of patients. While each story is unique, they are not that different from that of Mike, a patient I treated for acute leukemia.

Mike started feeling poorly in 2016, and a bone marrow biopsy revealed acute myeloid leukemia (AML). I began his initial treatment with aggressive chemotherapy, which caused difficult side effects and required him to spend more than a month in the hospital. After further therapy, Mike fully recovered, and he has been in remission for more than 2 years.

Mike, and patients like him, are our true partners in cancer research. They are the reason we do what we do.

We are in the midst of a historic moment in cancer research. Groundbreaking discoveries from multiple disciplines—epidemiology, pathology, molecular biology, medicinal chemistry, structural biology, data science, and others—have converged into remarkable advances and clinical benefits. These insights have triggered unprecedented industry investment, philanthropic support, and patient advocacy for cancer research. In addition, NCI has benefitted from concerted, sustained, and bipartisan support from Congress and the White House.

Norman E. Sharpless, M.D., with former patient Mike, whom he treated for acute leukemia in 2016.

As a result, patients today have better options for more effective and less toxic therapies than ever before. It is not a coincidence that death rates for most cancers are on a steady decline. And it's not by chance that the age-adjusted rate of new cancer cases is steadily decreasing.

Yet as we celebrate new successes, we face new and existing challenges. There are still too many cancers for which we lack effective screening and prevention, and others for which we lack effective therapies. Some new treatments are so expensive that they are inaccessible to many patients. Some cancer treatments have side effects that may be considered worse than cancer. The dissemination and implementation of effective treatments to the community setting can be slow and inconsistent.

We are tackling these issues head on.

As we prepare to overcome these obstacles, I have identified key areas of focus that leverage the scale and reach of NCI. These areas of focus, which permeate all sections of this *Annual Plan and Budget Proposal*, are to:

- Develop the workforce of cancer investigators
- Reaffirm our commitment to basic science to drive novel approaches and technologies
- Innovate the design, administration, and analyses of clinical trials
- Increase data aggregation and interpretation to speed work across the cancer enterprise

The pages that follow reveal a promising future for cancer research. These are times of great hope and great challenge. This *Annual Plan and Budget Proposal* lays out a vision to achieve our goals at an even faster rate. With this plan, we become ever closer to fulfilling NCI's mission to help all people live longer, healthier lives.

**Norman E. Sharpless, M.D.**
Director
National Cancer Institute

# KEY FOCUS AREAS

NCI is responsible for the full scope of cancer research—from conducting basic science on the biological mechanisms of cancer to developing prevention, early detection, and treatment approaches to improving public health and the lives of cancer survivors. Focusing on the following areas will catalyze additional progress in cancer research and take advantage of the opportunities described in this plan.

## Basic Science

**Reaffirm our commitment to basic science to drive novel approaches and technologies**

Basic science discoveries fuel new approaches to cancer prevention, detection, and treatment across cancer types and populations.

## Workforce Development

**Support the cancer research enterprise by focusing on the workforce of cancer investigators**

A diverse and talented workforce of cancer researchers will make the discoveries needed to better prevent, detect, and treat cancer.

## Big Data

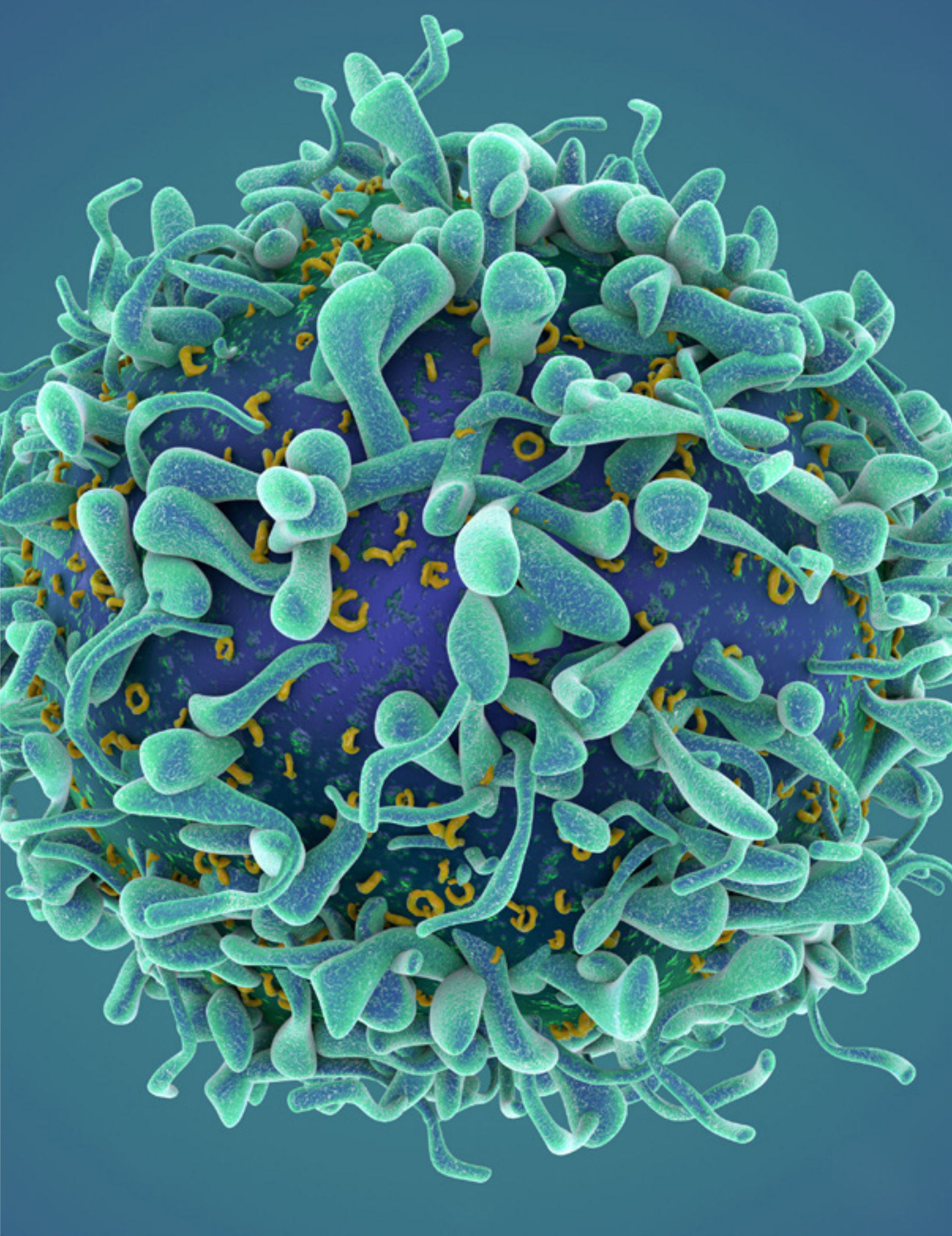
**Increase data aggregation and interpretation to speed our work across the cancer enterprise**

Harnessing the power of large and diverse scientific and clinical datasets holds incredible promise to accelerate research and improve patient care.

## Clinical Trials

**Fully realize the power of clinical trials through innovative design, administration, and analyses**

Clinical trials are a fundamental means for making progress in cancer care. Enhancing cancer clinical trials will mean that the success of new cancer interventions can be determined more rapidly.



## Edith—Pennsylvania

Clinical Professor, Sidney Kimmel Cancer Center, Thomas Jefferson University

# Leading the Nation's Progress against Cancer

NCI's mission is to lead, conduct, and support cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives. As the largest funder of cancer research in the world, NCI advances a broad portfolio of research—from basic science to the development of prevention, early detection, and treatment approaches to interventions to improve public health and survivorship.

## The Return on Cancer Research Investment

Federal investments in research have led to a substantial reduction in the burden of cancer in the United States. Today, people diagnosed with cancer live longer and enjoy a better quality of life than has ever been possible. Because of better prevention and screening, the age-adjusted rate of new cancer cases is also declining.

NCI collects and analyzes statistics on cancer incidence, mortality, and survivorship, so the progress we have made in reducing the burden of cancer among Americans can be measured. For example, these age-adjusted statistics show:

- The rates of death for all cancer types combined are declining among men, women, and children of all major racial and ethnic groups. From 1991 through 2015, the overall cancer death rate fell by 26.2%. In 2016 alone,

## Engaging Local Communities to Reduce Cancer Disparities

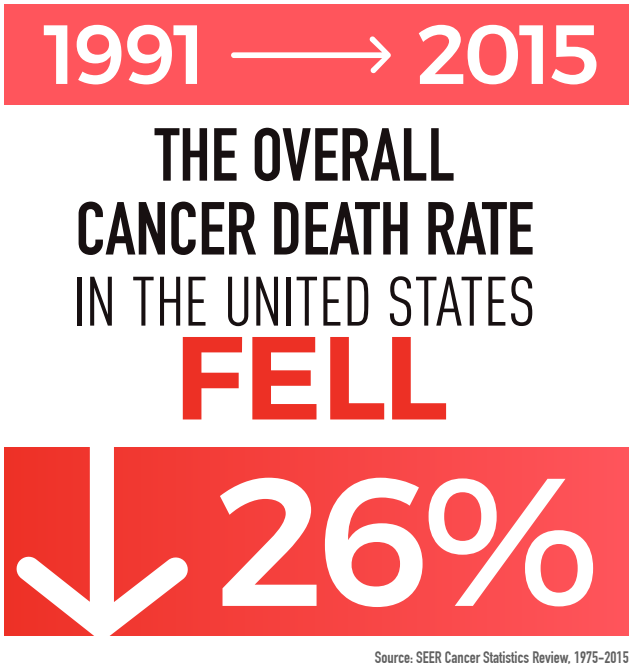
Edith Mitchell, M.D., developed a passion for medicine because of a doctor who cared for her great-grandfather at their farm north of Memphis, Tennessee. When 3-year-old Edith announced she wanted to be a doctor like him when she grew up, he told her she could be anything she wanted to be. She followed her dream and became a doctor.

While in medical school in the 1970s, Edith joined the US Air Force (USAF) and eventually became the first female physician in USAF history to attain the rank of brigadier general.

As an oncologist and researcher, Edith works to bring the latest treatments to communities that need them the most. "If we are unable to deliver care to at-risk populations in their neighborhoods, we will not succeed," she said. "We need to increase equal access to care."

Edith advocates engaging community physicians to address cancer disparities, an approach she lives by. For example, after holding focus groups with local communities, African American enrollment in her NCI-funded R01 trial on colorectal cancer reached 25%. This percentage is about four-times higher than average.

Edith developed patient education videos that promoted the screening and treatment of colorectal and breast cancers. The breast cancer video was televised during Black History Month, and 30,000 copies were distributed to doctors' offices across the United States. Also, at a patient education event, she followed her own advice of "knowing your audience" and gave her presentation in Spanish rather than English because of the number of Latinas in the audience.




Source: SEER Cancer Statistics Review, 1975–2015

the death rate from cancer was 1.7% lower than the rate in 2015.

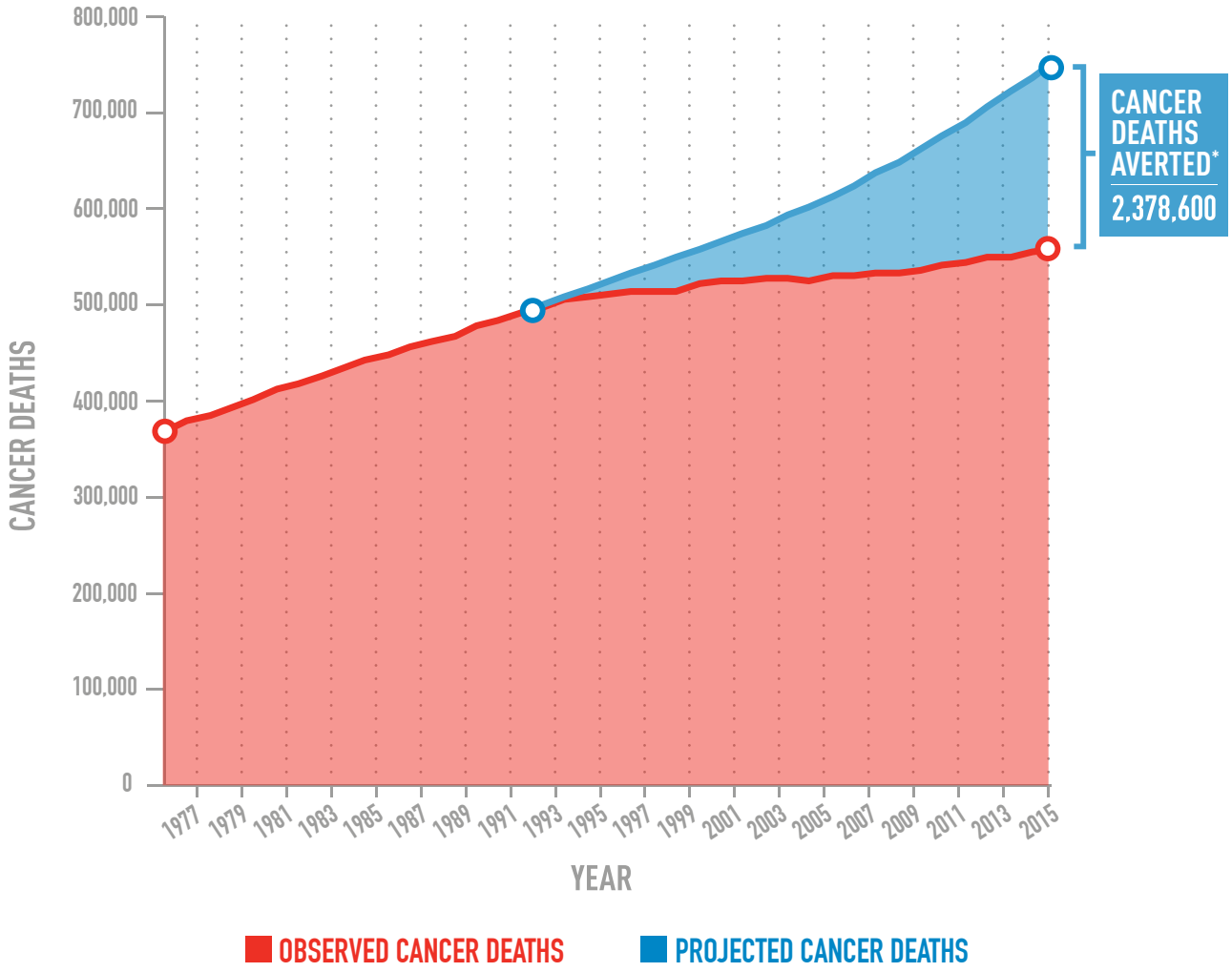
- The rate of new cancer cases is falling. From 2006 through 2015, the rate of new cancer cases fell by more than 1% each year. This trend stands in sharp contrast with the rising rate of cancer incidence before the beginning of the 21st century. However, the reduction in cancer incidence has not been equivalent for men and women. From 2006 through 2015, the rate of new cancers declined for men but was stable for women.
- The incidence and mortality rates of several cancer types have fallen significantly over time. These improvements vary by sex and race/ethnicity. For example, from 2011 through 2015, the decline in lung and bronchus cancer incidence among black men was 40% greater than that among white men. Among women, American Indians/Alaska Natives had the largest decline in lung and bronchus cancer incidence, with a decline 80% greater than that observed among white women. During the same period, the decline in lung and bronchus cancer mortality among black men was 63% greater than that among white men. Black women also had the largest decline in lung and bronchus cancer mortality, with a decline 50% greater than that observed among white women.

## The Need for Greater Progress

These trends are encouraging, but important work remains. Too many people are still diagnosed with cancer and die from it. Many survivors of cancer experience serious late effects of the disease and its treatment. Progress has not been uniform for all types of the disease, and not all groups of people have benefited equally from advances in cancer care. Some indicators of the need for greater progress are described below.

- It is estimated that more than 1.7 million adults in the United States will be diagnosed with cancer in 2018, and more than 600,000 (i.e., more than one person every minute) will die from it. As the population ages, the numbers of new cancer cases and deaths among adults will continue to grow.
- Cancer is the most common cause of death from disease in children and adolescents ages 1 to 19 in the United States. While deaths from childhood cancer have been declining steadily since the 1970s, the incidence of childhood cancer has been slowly increasing over the same period. In 2018, nearly 16,000 new cases of cancer and approximately 2,000 cancer deaths will occur among US children and adolescents.
- Too many cancers are still not preventable, readily detectable, or curable. Several deadly types of cancer, including pancreatic, ovarian, and lung and bronchus cancers, are often diagnosed at late stages because they do not cause early symptoms, and no effective screening tests are available to detect them early. In addition, current treatments for some cancer types, such as pancreatic, liver, and high-grade brain cancer, are not very effective. The death rates for some cancers, such as liver and uterine cancer, are increasing in the United States.
- Specific populations, including certain racial/ethnic groups and rural populations, suffer disproportionately from some cancers. Reasons for these disparities include inadequate access to cancer screening tests and quality cancer care. Research indicates that genetics, modifiable risk factors (e.g., tobacco smoking and excess body weight), and environmental exposures are also important.

# Cancer Deaths Averted in Men & Women from 1991 to 2015




* Represents the difference between the number of observed cancer deaths and the number of projected cancer deaths that would have occurred had cancer death rates remained at their peak.

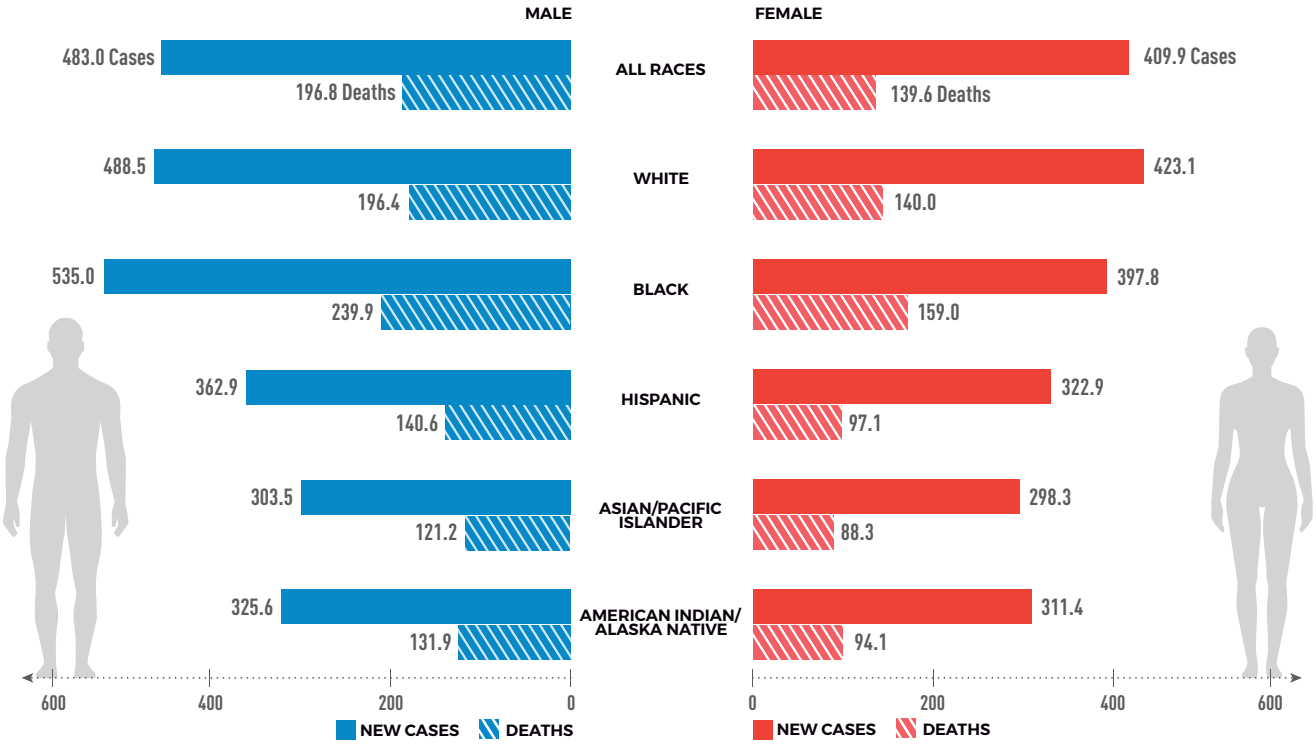
Adapted from: Siegel RL et al, Cancer Statistics, 2018. CA Cancer J Clin 2018;68:7–30. John Wiley & Sons, Inc. © 2018 American Cancer Society

More research is needed to better understand and mitigate the effects of both biological and nonbiological factors that contribute to cancer disparities. Read how NCI-funded researcher Edith Mitchell from Pennsylvania is working to reduce cancer disparities on page 5.

- Cancer is a growing global health burden. Worldwide, more than 21 million new cases of cancer are predicted to occur in 2030, an increase of 24% over the 17 million cases that occurred in 2016. It is also predicted that 13 million cancer deaths will occur in 2030, an increase of nearly 44% over the 9 million cancer deaths reported in 2016. Most of this growing burden of cancer incidence and mortality will be borne by low- and middle-income countries.

## Number of New Cancer Cases and Deaths Each Year

Per 100,000 Persons by Race/Ethnicity & Sex: All Cancers




Source: SEER 18, 2011–2015

# 2016 ⟶ 2030

## WORLDWIDE CANCER CASES ARE PROJECTED TO INCREASE

**↑ 24%**

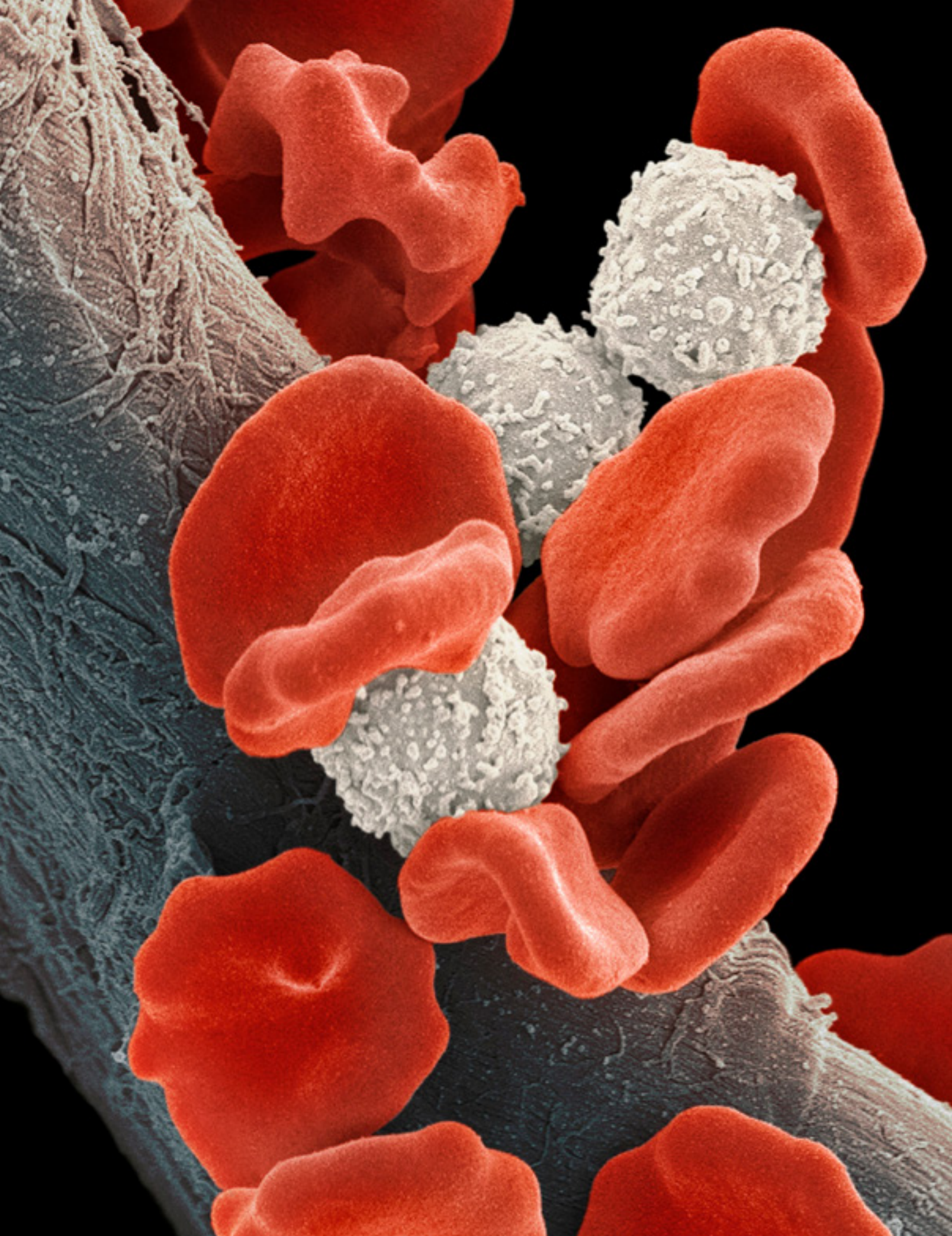
FROM **17 million** TO **21 million**

## WORLDWIDE CANCER DEATHS ARE PROJECTED TO INCREASE

**↑ 44%**

FROM **9 million** TO **13 million**

Sources: American Cancer Society: Global Cancer Facts & Figures, Third Edition, 2015. Global Burden of Disease Cancer Collaboration: JAMA Oncology, June 2, 2018 [Epub ahead of print].



## Zach—Pennsylvania

Anaplastic large cell lymphoma survivor

# Understanding the Mechanisms of Cancer

Virtually all major advances against cancer, including the newer molecularly targeted therapies, immunotherapies, and interventions to prevent cancer, had their origins in earlier discoveries made in the basic sciences. Many of these discoveries were made in areas such as cell biology, molecular biology, genetics, and immunology, where practical applications to cancer medicine could readily be conceived. Other areas, such as physics, mathematics, materials science, and computational sciences, have also helped to advance cancer research. Although cancer-related applications of discoveries in these latter areas were less immediately obvious in most cases, they contributed to the development of the advanced technologies and analytical methods that are essential to cancer research and clinical oncology today.

NCI's funding of basic research has led to major advances in cancer genomics, which has enabled the development of new precision medicines and other approaches for cancer prevention, detection, and treatment. Yet, our knowledge of other fundamental mechanisms of cancer remain much less complete. For example, we need to increase our understanding of how normal cells become cancerous, how the tumor microenvironment influences cancer development and progression, how cancers evade attacks by the immune system, and the role of aging in cancer. Achieving a better understanding of these mechanisms will only be possible through additional basic research.

One of the best ways NCI supports basic research is through research project grants, which fund the vast majority of investigator-initiated science. The knowledge gained from this research will drive

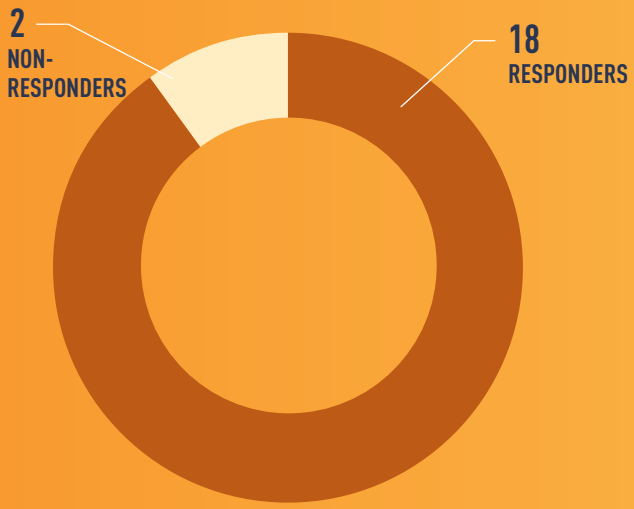
## Hitting a Home Run with an Investigational Drug

Thirteen-year-old Zach had a great day in August 2017, when he caught a home run hit by Tommy Joseph at a Philadelphia Phillies game and later met him for a ball signing. Zach's mother, Pam, watched with pride, a marked contrast from her anguish 7 years earlier when Zach had been diagnosed with anaplastic large cell lymphoma (ALCL).

Zach had a difficult time with his chemotherapy and relapsed halfway through treatment. His doctors proposed an NCI–Children's Oncology Group clinical trial of crizotinib (Xalkori), a drug that targets mutations in a gene called *ALK* and that has been used successfully against certain lung cancers.

Within 3 days of starting crizotinib, Zach transformed back to the high-octane boy his family knew best. His tumors shrank over time, and his doctors still find no evidence of cancer. An avid althete in school and youth leagues, Zach dreams of hitting his own home runs as a professional baseball player. In Pam's eyes, crizotinib has already been a home run. "This is a drug that saved my boy's life," she reflected gratefully.

### PHASE 2 CLINICAL ACTIVITY OF CRIZOTINIB IN ALCL




Source: Mossé YP et al. J Clin Oncol. 2017 Oct 1;35(28):3215–21.

tomorrow's advances to help patients with cancer and individuals at risk of the disease.

**Vision**

*Researchers will have a comprehensive understanding of cancer biology that catalyzes the development of newer and safer ways to prevent, detect, diagnose, and treat cancer.*

**Approach**

- *Develop a comprehensive understanding of the molecular and cellular basis of cancer.*
- *Understand how cancer cells interact with normal cells in the body to support or suppress cancer development and progression.*

*The Cancer Genome Atlas determined the major molecular characteristics of 33 of the most common types of cancer.*

## Progress in Understanding the Mechanisms of Cancer

Acquiring a comprehensive understanding of the molecular changes that drive the development and progression of malignant tumors has been a long-sought goal in cancer research. A major step toward this goal was achieved by The Cancer Genome Atlas (TCGA), a program jointly sponsored by NCI and the National Human Genome Research Institute, which is also part of NIH.

TCGA determined the major molecular characteristics of 33 of the most common types of cancer through an in-depth analysis of tumor specimens from more than 10,000 patients. The findings from TCGA have led to a new understanding of cancer at the molecular level and expanded tumor classification beyond the organ or tissue type to include cancer subtypes based on their molecular features (e.g., the four major molecular subtypes of female breast cancer: luminal A, luminal B, triple-negative basal-like, and HER2-expressing).

TCGA data are publicly available for further analyses through NCI's Genomic Data Commons (GDC), one of multiple repositories that will allow NCI to build a Cancer Research Data Commons. Information from TCGA and from other research has also informed the design of newer research programs, such as the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) and NCI–Children's Oncology Group Pediatric MATCH clinical trials.

Other NCI-funded research has provided an initial understanding of how communication between cancer cells and other cells in the body contributes to cancer cell growth, how the plasticity of cancer cells can lead to their becoming resistant to specific treatments, and how cancer cells and immune cells interact to either promote or suppress tumor growth and progression. A few notable recent accomplishments on the mechanisms of cancer are described below.

### Comparing the Molecular Features of Different Cancers

Comparing the molecular characteristics of different types of cancer can provide a better understanding of their similarities and differences and improve tumor classification, both of which will inform the development of new treatments and future clinical trials. In 2018, a consortium of international and NCI-funded researchers reported the results of a cross-tumor-type analysis of TCGA data and the corresponding clinical information.

The findings from this massive undertaking fell into three main categories: 1) cell-of-origin patterns, 2) oncogenic processes, and 3) cell signaling pathways. In the first category, the data suggest that different tumor types can be clustered according to the type of cell from which they are thought to have originated, a finding that increases our understanding of how the tissue in which a cancer arises can influence its molecular characteristics. The data in the second category provide a broad view of the molecular processes at the genomic level that drive cancer development and progression. Finally, the data in the third category detail the alterations in cell signaling

pathways that cancer cells use to support their continued growth and survival.

Overall, this work will aid in the development of new treatments for a wide range of cancers. Read about how childhood cancer survivor Zach from Pennsylvania has benefited from a treatment that targets alterations of the *ALK* gene, which occur in more than one cancer type, on page 11.

## Investigating How Cancer Cells Communicate with Normal Cells

Research has shown that cancer cells communicate with nearby normal cells and frequently co-opt some of their functions to support tumor growth and progression. However, a detailed understanding of the communication channels and mechanisms used by cancer cells is needed. NCI funding is helping to advance research in this area.

In 2017, an international team of NCI-funded investigators at Cold Spring Harbor Laboratory in New York and their colleagues demonstrated that pancreatic tumors induce different physiological responses from fibroblasts (connective tissue cells) that are closest to them than from fibroblasts that are farther away. They also showed that this pattern of responses was maintained when the locations of the fibroblasts were switched. The researchers concluded that the fibroblasts closest to a tumor are influenced by direct interactions with cancer cells, whereas fibroblasts farther away are influenced by factors secreted from cancer cells that diffuse toward them. Fully understanding these short-range communication mechanisms may reveal vulnerabilities that can be exploited therapeutically to block tumor growth.

In another NCI-funded study conducted in mice and humans, researchers showed that signals sent by lung tumors via the bloodstream trigger the migration of a certain class of neutrophils (white blood cells) from the bones to the tumors, where they exhibit cancer-promoting properties. Acquiring a detailed understanding of this long-distance communication mechanism may also reveal opportunities to disrupt tumor growth.

## Identifying Elements that Suppress Antitumor Immunity

Antitumor immune responses are carried out primarily by cytotoxic T lymphocytes, or killer T cells. The activity of these cells can be inhibited in a variety of ways as part of normal regulation of the intensity and duration of immune responses. However, some of these normal inhibitory mechanisms can be co-opted by tumors to help cancer cells evade immune destruction.

Recently, scientists in NCI's intramural research program discovered that two essential elements in the tumor microenvironment, namely oxygen and potassium, can be exploited to suppress cytotoxic T-cell activity. T cells of all types contain oxygen-sensing proteins called PHD proteins. When elevated amounts of oxygen are present, as in the lungs, the activity of these proteins creates an immunosuppressive environment that promotes tumor growth. Correspondingly, the dead and dying cells within tumors release potassium into the tumor microenvironment, increasing the extracellular concentration of this element, which suppresses cytotoxic T-cell activity. Ongoing research is focused on developing strategies against these and other mechanisms that inhibit antitumor immune responses.

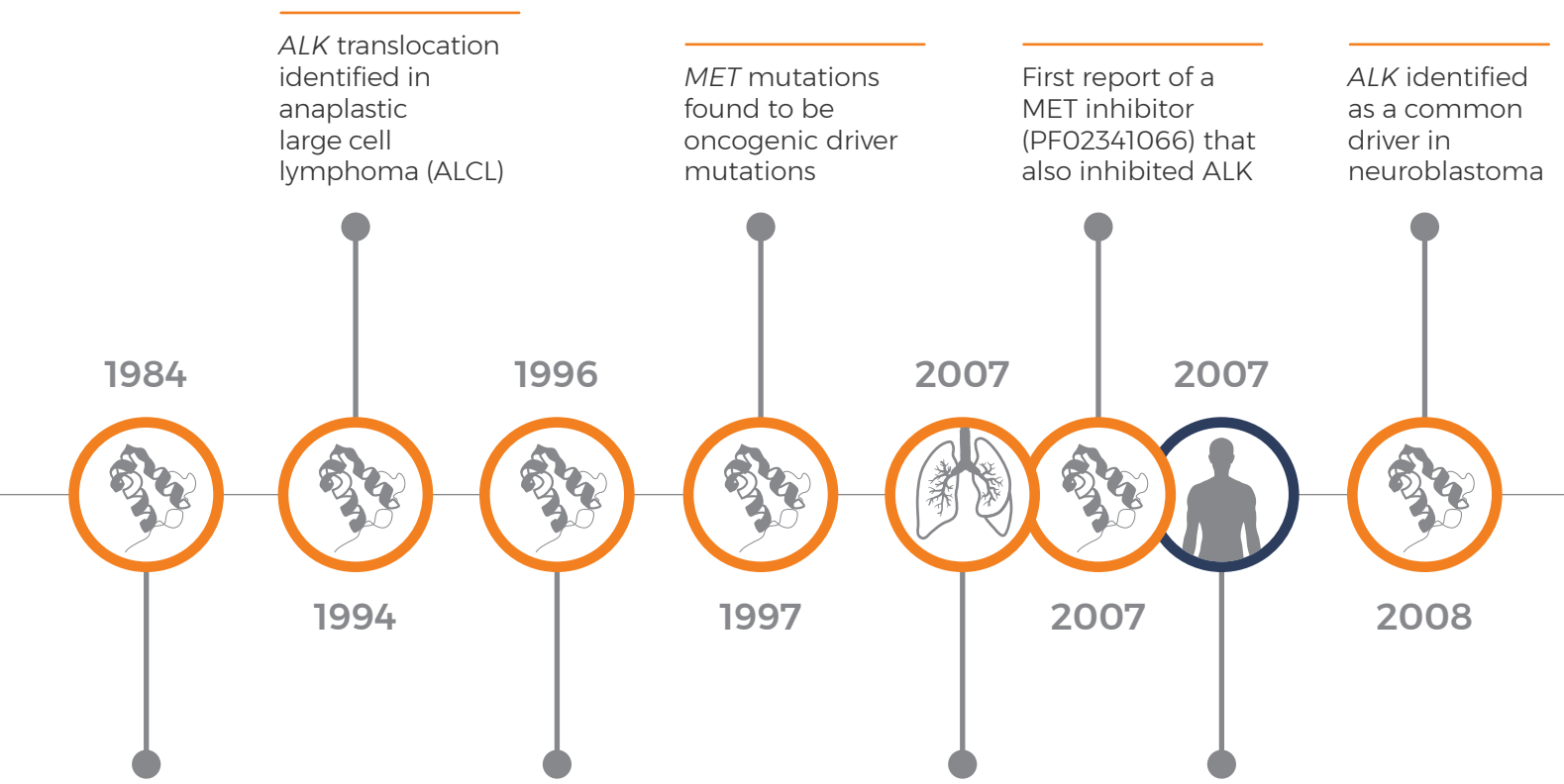
*Ongoing research is focused on developing strategies against mechanisms that inhibit antitumor immune responses.*

## Exploring the Biology of Fusion Oncoproteins

Fusion proteins are created by the joining, or fusion, of two separate genes that encode different proteins. They are commonly found in cancer, especially in childhood cancers, and they often drive tumor development. When fusion proteins contribute to tumor formation, they are called fusion oncoproteins. Because of their important role in driving cancer development, understanding the biology of these oncoproteins and finding ways to inhibit their activities is a major priority

# Why Invest in Basic Science?

## Development of a Targeted Therapy

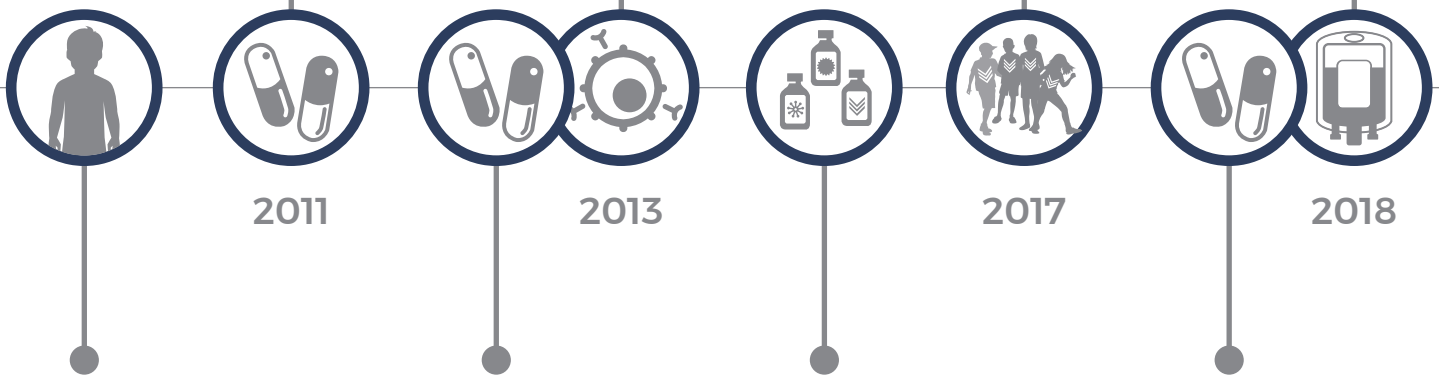



**BASIC RESEARCH** **CLINICAL TRIALS**

Progress against cancer requires long-term investments in basic research, which lay the foundations for tomorrow's clinical advances. Research that leads to a new treatment or intervention usually involves a process that spans years or even decades before patients benefit.

The development of the cancer drug crizotinib (Xalkori) is one such example. Crizotinib was initially developed to target the protein produced by the oncogene *MET*. It was later found to also inhibit the proteins produced by oncogenic forms of the *ALK* gene, which have been found in anaplastic large cell lymphomas (ALCL) and some non-small cell lung cancers (NSCLC) and neuroblastomas. NCI-funded basic research identified these targets and revealed their biological importance in cancer development and progression.

The arc of scientific discovery leading to the first Food and Drug Administration approval of crizotinib for NSCLC spanned a period of nearly 30 years. Clinical testing of the drug for additional molecular subtypes of NSCLC, ALCL, and neuroblastoma continues today.



**2009**

Children's Oncology Group (COG) opens trial for crizotinib (PF02341066) in pediatric refractory solid tumors and ALCL

**2011**

Results from PROFILE 1001 lead to accelerated FDA approval of crizotinib (Xalkori) for treatment of ALK-positive NSCLC

**2013**

FDA approves crizotinib for ALK-positive locally advanced or metastatic NSCLC

**2013**

Results from COG trial show crizotinib has antitumor activity in patients with some solid tumors and ALCL

**2015**

NCI-MATCH precision medicine trial opens with *MET* and *ALK* gene alterations as targets for treatment with crizotinib

**2017**

Pediatric MATCH trial opens with *ALK* as one of the gene alterations being targeted

**2018**

FDA grants breakthrough designation to crizotinib for ALCL

**2018**

COG launches phase 3 trial with crizotinib in combination with chemotherapy for high-risk neuroblastoma patients

*"Discoveries in basic science propel progress for patients."*

—NCI Director Norman Sharpless, M.D.

in cancer research, as well as a goal of the Cancer Moonshot℠.

In 2017, NCI-funded researchers at the University of Texas Health Science Center in San Antonio reported findings from a study of the fusion oncoprotein EWS-FLI1, which drives approximately 85% of Ewing sarcomas. These tumors occur mainly in children and young adults and are found most often in the bones.

The researchers discovered that EWS-FLI1 increases tumor cell production of an enzyme called pappalysin-1 (PAPPA), which breaks down certain proteins called insulin-like growth factor binding proteins (IGFBPs). The breakdown of IGFBPs releases the hormone insulin-like growth factor into the local environment, where it promotes cancer cell growth.

Using cell and animal models, the researchers also showed that inactivating PAPPA might be an effective strategy in treating Ewing sarcoma. Increased funding for basic research on this and other fusion oncoproteins should lead to new treatment approaches for pediatric and adult cancers.

*Advances in biomedical and computing technology are giving us the tools to greatly increase our understanding of cancer biology.*

## Opportunities for Greater Progress

Advances in biomedical and computing technologies are giving us the tools to greatly increase our understanding of cancer biology. For example, scientists can now image and study individual structures and molecules inside cells, including living cells, at unprecedented levels of resolution. Despite these advances, there is still much more that we need to learn. Enhanced focus on the following areas of opportunity will enable greater progress against cancer.

### Creating Four-Dimensional Maps of Human Tumors

Tumors are ecosystems that contain a variety of cell types, including cancer cells, immune cells, tumor-associated normal cells (fibroblasts, or stromal cells), vascular cells, and neural cells. These ecosystems evolve continuously during tumor development, progression, and in response to treatment.

In addition, the cancer cells in separate regions of a single tumor can differ from one another in important ways—a phenomenon known as tumor-cell heterogeneity—and both cellular and noncellular components of a tumor's microenvironment can influence a tumor's behavior (e.g., its aggressiveness or its responsiveness to treatment).

Given the need for a more comprehensive understanding of the molecular, cellular, and tissue alterations that drive cancer's development and progression, the Cancer Moonshot is supporting the Human Tumor Atlas Network to construct detailed maps, or atlases, of the various components of tumors and their interactions over time for specific pediatric and adult cancers.

The Pre-Cancer Atlas, which is described in this plan in *Preventing Cancer* on page 20, is part of this effort. In addition to providing important insights into the initiation and evolution of tumors, these atlases will also inform the development of new approaches to cancer prevention and treatment.

### Investigating the Role of Microbiomes in Cancer

Populations of bacteria, fungi, and viruses—collectively known as microbiomes—inhabit the skin, colon, mouth, and other tissues of the body, as well as some types of tumors. Some members of these microbial populations have been implicated in cancer development and in the effectiveness of cancer treatments. For example, NCI-supported researchers and others have shown that the composition of the intestinal microbiome can influence a tumor's response to immunotherapy and that the bacteria in some pancreatic cancers can inactivate the chemotherapy drug gemcitabine (Gemzar).

There is still much more to learn about how microbiomes influence cancer-related processes, immune responses, and the effectiveness of cancer treatments. Specifically, we need to identify the relevant microbial species and the mechanisms by which they exert their effects. In the future, we may be able to modify the compositions of microbiomes to reduce cancer risk and optimize the effectiveness of cancer treatments without causing additional adverse effects.

## Understanding Aging and Cancer

The greatest risk factor for cancer is advancing age. Accordingly, several processes associated with aging have also been linked with cancer development, including reductions in DNA repair capacity and immune function, a decline in the regenerative capacity of stem cells to replenish the body's tissues, and the accumulation of nondividing, metabolically active (i.e., senescent) cells in tissues, which may secrete factors that promote chronic inflammation.

Additional support for research on the basic mechanisms of aging and cancer will enhance our understanding of both subjects and enable the development of new strategies for cancer prevention and treatment, as well as the optimal delivery of cancer interventions based on a person's age. A critical unmet need in this area of research is the development and use of age-appropriate animal models. Studies to examine the effects of aging on the efficacy and toxicity of current cancer therapies are also a high priority to ensure that contemporary cancer patients can be stratified, as needed, to receive age-appropriate care, which may necessitate the development and administration of different treatment approaches for older patients.

*Research on the basic mechanisms of aging and cancer will enable the development of new strategies for cancer prevention and treatment.*

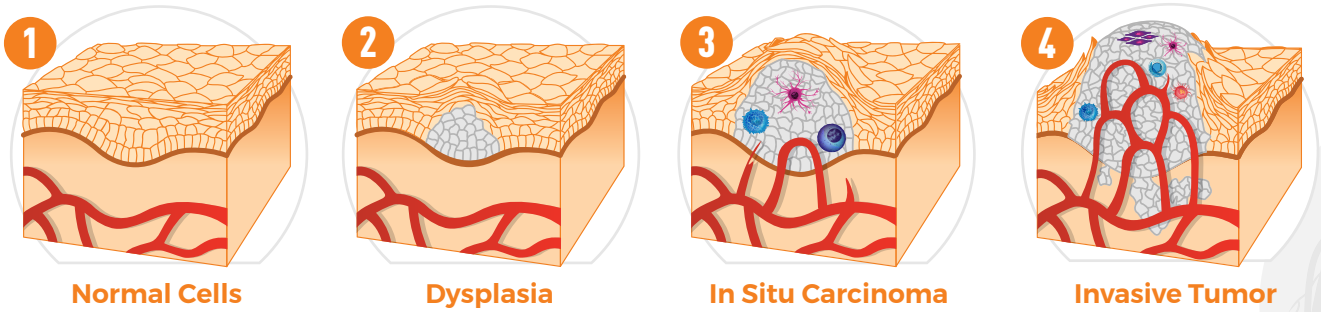
## Defining the Role of Nuclear Architecture in Cancer

The term nuclear architecture refers to the structural organization, including the compartmentalization, of the components of a cell's nucleus. This architecture is both complex and dynamic, changing as needed to carry out and regulate vital processes in the nucleus, such as DNA replication, DNA repair, and RNA transcription and processing. Defects in genomic organization and nuclear architecture have been linked to numerous human diseases, including cancer, neurodegenerative disorders, and muscular dystrophies, and they recently have been associated with human aging.

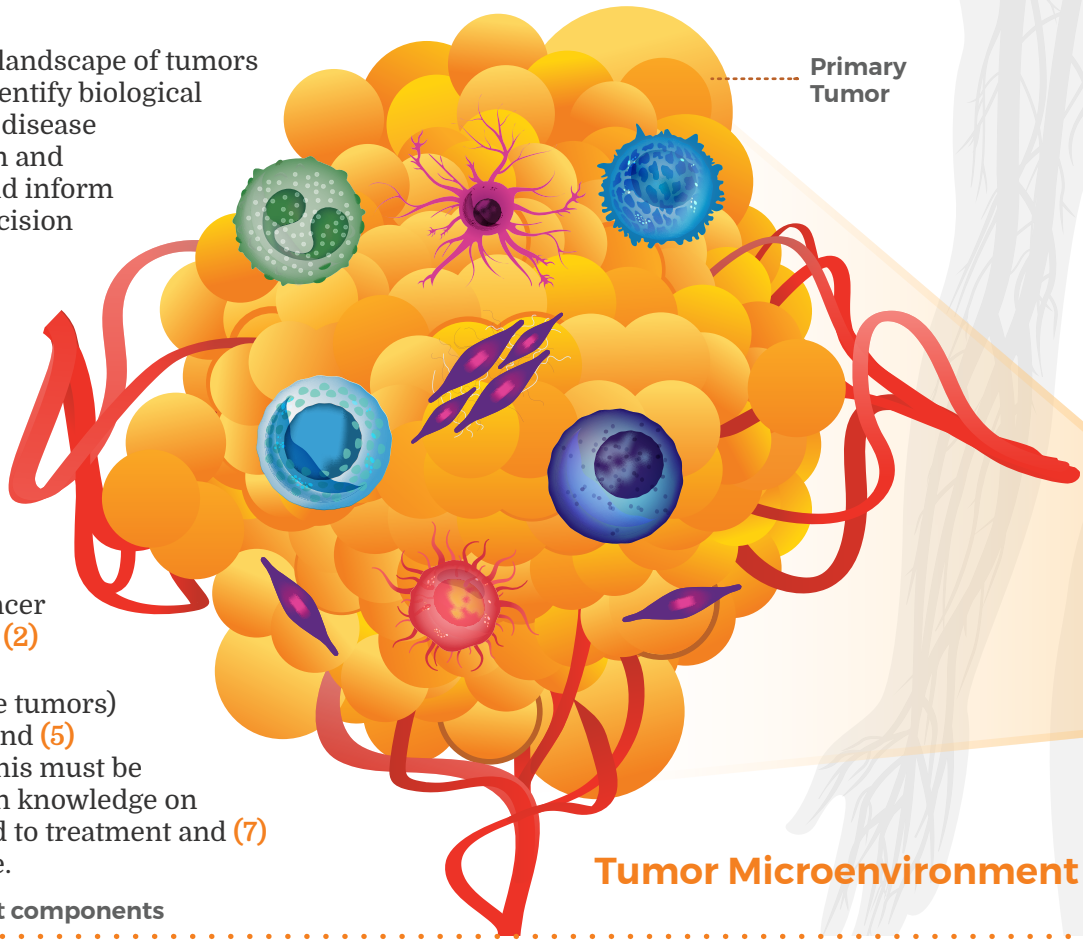
The development of advanced microscopy and imaging technologies, such as high-throughput chromosome territory mapping (HiCTMap) and Fourier phase-based depth-resolved nanoscale nuclear architecture mapping (nanoNAM), is providing new opportunities to investigate genomic organization and nuclear architecture at unprecedented levels of resolution. This research will lead to a greater understanding of both normal physiological processes and disease at the cellular level, and it may also identify important new targets for future cancer therapies. Additional funding will accelerate progress in this area.

# Cancer and the Human Tumor Atlas Network

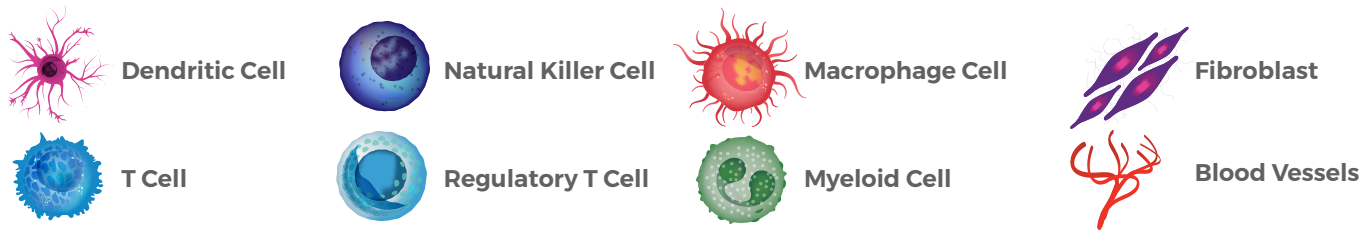
The construction of human tumor atlases will provide a more comprehensive understanding of the ecosystems of tumors at the macro- and the micro-level. NCI has established the Human Tumor Atlas Network (HTAN) for this purpose.




Mapping the landscape of tumors will help identify biological markers of disease progression and treatment resistance and inform the development of precision risk-stratification, prevention, screening, diagnostic, and treatment strategies. To accomplish this, a better understanding of the molecular-, cellular-, and tissue-level communication networks that drive the major transitions in cancer from (1) normal cells to (2) dysplasia to (3) *in situ* carcinoma (noninvasive tumors) to (4) invasive disease and (5) metastasis is needed. This must be integrated with in-depth knowledge on how tumors (6) respond to treatment and (7) develop drug resistance.

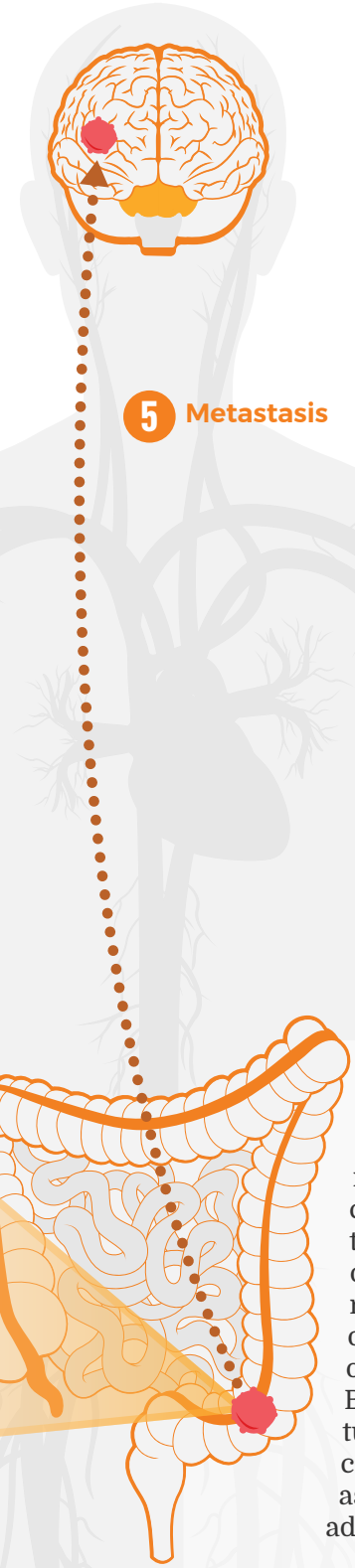


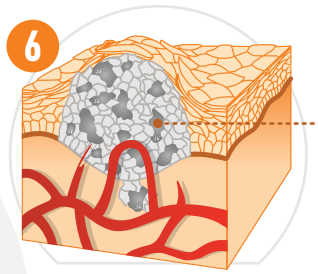

**Tumor Microenvironment components**



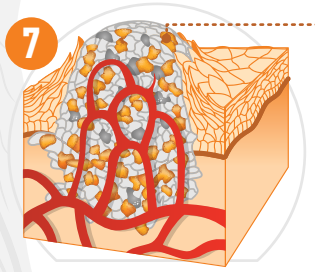
## Multilevel Network Analyses & Data Integration

Human tumor atlases will show the tissue, tumor, cell, and molecular level interactions of cancer. Computer modeling and data integration of this multilevel information will allow for the creation of dynamic visual resources of tumor evolution.




Responding to Treatment




Developing Drug Resistance

This information must be accompanied by a more complete understanding of the differences (heterogeneity) of cancer cells within tumors, the role of heterogeneity in tumor evolution, and the contributions of the noncancerous components of tumors in the microenvironment. The emergence of powerful new technologies and computational methods has put a comprehensive understanding of tumor ecosystems within our reach. Therefore, one recommendation of the Cancer Moonshot℠ Blue Ribbon Panel was to develop 4-dimensional tumor atlases to document the molecular and cellular alterations and interactions within tumors as they evolve from precancerous lesions to advanced cancers.

To address this recommendation, NCI has established HTAN, which will focus initially on select adult and pediatric cancers. Each of the HTAN research centers will construct pilot-scale human tumor atlases describing important transitions in cancer: the transition from premalignant to malignant, the transition from locally invasive to metastatic disease, the dynamics of patient response to treatment, and the development of resistance to therapy. In addition, an HTAN Data Coordinating Center will collect, store, curate, and disseminate all data, tools, computational models, and completed atlases.

Tumor cells communicate with other cells, both locally and distantly. The organ- and tissue-level communication networks that support tumor development, growth, and metastasis can be mapped and integrated with analyses at multiple levels.

Cancer development, progression, and metastasis require complex interactions within the local tumor microenvironment that are mediated by many factors. These interactions can be mapped spatially and temporally in a tumor atlas.

Molecular networks are systems of interacting molecules (i.e., genes, proteins, etc.) that underlie specific biological functions. These intracellular networks can be mapped in all cells in the tumor microenvironment for integration into an atlas.

Cancer cells have genetic and epigenetic alterations that influence the organization and expression of genes. These alterations and their effects on cancer cells can be mapped and integrated with other-level analyses in a tumor atlas.

Credit: University of Utah Health

## Gregg—Utah

Familial adenomatous polyposis patient

# Preventing Cancer

Cancer prevention is a critical component of our effort to reduce the burden of cancer in the United States and globally. As a measure of its importance, cancer prevention has the potential, in the long run, to save even more lives than treatment. Effective prevention will also reduce cancer incidence and morbidity, meaning fewer people will have to face the physical, financial, social, and psychological harms of a cancer diagnosis and treatment.

One approach to cancer prevention is reducing or eliminating exposures to cancer-causing substances in the environment, such as asbestos, tobacco smoke, and radon gas. Another approach is to protect the body against such exposures or reduce their effect. For example, using sun screen to protect the skin against ultraviolet radiation and getting vaccinated against cancer-causing viruses, including certain types of human papillomavirus (HPV) that cause cervical and several other types of cancer, can protect against processes that can eventually lead to cancer. In addition, some cancer screening tests, such as the Pap smear for cervical cancer and colonoscopy for colorectal cancer, can aid in cancer prevention. These tests detect premalignant lesions that can be removed or destroyed before they progress to cancer.

Reasearch in the field of cancer prevention is often not feasible in the private sector due to the many economic, logistical, and scientific challenges that must be overcome. Therefore, NCI's commitment to cancer prevention research is particularly

## Leveraging Biology to Prevent Familial Colon Cancer

Colon cancer has run in Gregg's family for generations, and it caused his mother's death when she was only 47 years old.

No one knew why the risk of this cancer was so high in his family or how to prevent it. All that changed in 1991, when NCI-funded researchers identified the *APC* gene, which, when mutated, greatly increases the risk of colon cancer. They used the Utah Population Database to trace the mutated gene to a family that had settled there in the 1850s.

It turned out that Gregg and half of his relatives had the *APC* mutation and a condition called familial adenomatous polyposis (FAP), in which numerous polyps form in the colon beginning at an early age. In the past, Gregg's colonoscopies typically revealed hundreds of polyps, with dozens of advanced ones that needed to be removed.

Recently, he participated in an NCI-funded phase 2 clinical trial at the Huntsman Cancer Institute at the University of Utah evaluating whether a combination of the drugs erlotinib (Tarceva) and sulindac could reduce the burden of polyps in people with FAP. The treatment worked. Gregg recalled that at the end of the trial his polyps had shrunk so much that "the doctors couldn't see them anymore."

He is thankful for this research, which gives him, his family, and many others greater hope for the future. "I get to play a small part in this progress," reflected Gregg.

PEOPLE WITH FAP HAVE A

**100%**

LIFETIME RISK OF

COLON CANCER

Source: Gala M and Chung DC. Semin Oncol. 2011 Aug;38(4)490–9.

important. In addition to supporting basic and translational prevention research, NCI supports cancer prevention clinical trials through programs such as the NCI Community Oncology Research Program (NCORP), a national network that brings prevention trials to communities across the United States. The return on NCI's investments in cancer prevention can be seen in the declining incidence and mortality of several types of cancer, most notably lung, colorectal, and cervical cancer.

Although we have made tremendous progress in cancer prevention, many opportunities lie before us to make even greater progress. Just as we are increasingly able to identify the best treatments for a person's cancer based on the genetic abnormalities of their tumor, fully characterizing a person's genetic makeup and understanding their environmental exposures over time should enable us to tailor personalized measures to screen for and prevent cancer. This is what we refer to as "precision prevention."

**Vision**

*A person's cancer risk will be known and effectively reduced.*

**Approach**

- *Identify and study risk factors for cancer, including personal and environmental risk factors.*
- *Develop and test new methods of cancer prevention, including drugs for chemoprevention, vaccines for immunoprevention, and behavioral strategies for risk reduction.*
- *More effectively implement existing cancer prevention methods, both in general and based on an individual's risk.*

## Progress in Preventing Cancer

NCI funding has supported major advances in cancer prevention, including the development of a hepatitis B virus vaccine to prevent liver cancer; demonstration that the drugs tamoxifen and raloxifene can reduce the risk of breast cancer in women at increased risk of the disease; and development of HPV vaccines to prevent the majority of cervical, vaginal, vulvar, anal, rectal, oropharyngeal (throat), and penile cancers. Recent NCI-funded research accomplishments are highlighted below.

### Screening for Barrett Esophagus to Prevent Esophageal Cancer

The incidence of esophageal adenocarcinoma (EAC), the most common form of esophageal cancer in the United States, has been increasing for the past four decades, particularly among white men. Most patients diagnosed with EAC have a poor prognosis, with a 5-year relative survival rate of 17%. The only established precursor for EAC is Barrett esophagus (BE), a condition that affects an estimated 1%–5% of the general population and is typically diagnosed in individuals with chronic acid reflux symptoms. However, a prior history of BE has been documented in only a minority of patients who develop EAC. The progression of BE to EAC occurs at a rate of less than 1% per year; therefore, most people with BE require only infrequent endoscopic monitoring to check for disease progression.

In 2018, NCI-funded researchers reported that, among individuals whose BE progressed to EAC, most had high levels of genomic abnormalities detected in their BE lesions 4 years before the development of cancer. This finding could provide doctors an opportunity to intervene to destroy these lesions and prevent EAC. In 2018, another NCI-supported research team led by investigators at Case Western Reserve University in Ohio used an experimental, swallowable, balloon-like sampling device to check esophageal tissue for modification (i.e., methylation) of the DNA in two genes, *CCNA1* and *VIM*, each of which is a biomarker for BE. The researchers proposed that this approach could be a cost-effective, sensitive, and well-tolerated way of screening for BE in at-risk individuals.

### Preventing Lung Cancer with a Vaccine

Lung cancer, the leading cause of cancer death worldwide, currently accounts for about 25% of all cancer deaths in the United States. Up to 30% of

human lung cancers are driven by mutations in the *KRAS* gene, almost all of which cause a change in amino acid 12 or 13 of the KRAS protein sequence.

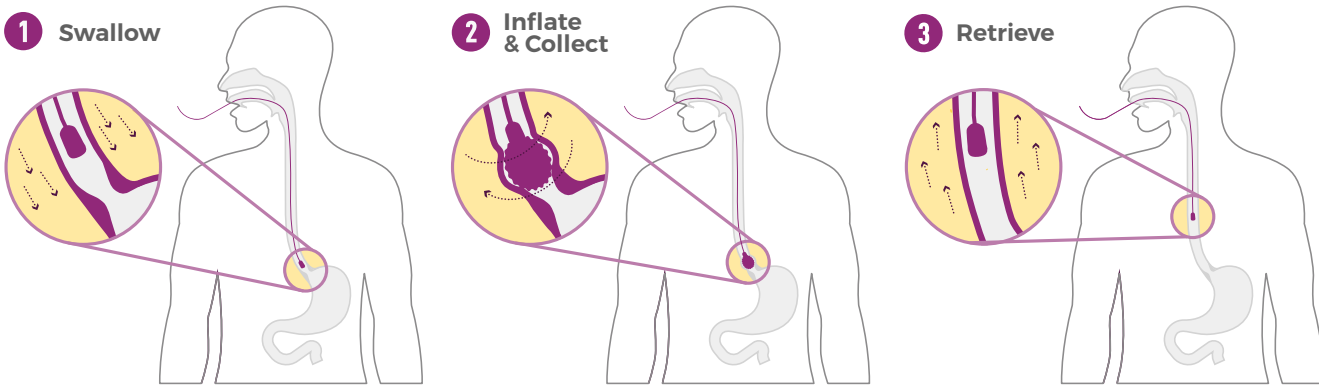
In 2017, NCI-funded researchers at the Medical College of Wisconsin and the NCI intramural research program reported the development of an experimental vaccine that targets KRAS protein bearing one of these mutations; specifically, at position 12 of the protein sequence, the amino acid glycine is replaced by the amino acid aspartate. This mutant protein is called KRAS G12D. In a mouse model in which the mutant protein can be activated, administering the vaccine before activating the mutant protein reduced both the number of lung tumors that formed and tumor size by more than 80% without adverse effects.

Although preliminary, these findings suggest that a vaccine to prevent KRAS G12D-driven lung cancers or to prevent their recurrence may be feasible. In addition, such a vaccine may prove useful in preventing the development or recurrence of the approximately 15% of colorectal cancers that are also driven by KRAS G12D. The results should also encourage the development of additional vaccines that target this and other mutant KRAS proteins.

## Preventing Polyp Formation in Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is a hereditary condition that predisposes individuals to the development of numerous polyps in the gastrointestinal tract and increases their lifetime risk of several cancer types, including a 100% risk of colorectal cancer and a 5%–12% risk of cancer of the duodenum (i.e., the upper part of the small intestine).

## How the Swallowable Balloon Device Helps Detect Barrett Esophagus




1 Swallow

Instead of undergoing standard endoscopy, patients can swallow a pill-sized capsule attached to a thin silicone catheter. The capsule passes through the esophagus and stops near the stomach.

2 Inflate & Collect

Once the capsule nears the stomach, a balloon with a textured surface is inflated and maneuvered to swab the lower esophagus, where Barrett esophagus (BE) typically begins. A sample of the cells lining the lower esophagus is collected.

3 Retrieve

The balloon is deflated through the catheter and inverted back into the capsule, thus protecting the sample from dilution or contamination. After retrieving the capsule through the mouth, DNA i extracted from the balloon's surface for a DNA methylation test.

**Device capsule and catheter in comparison to a vitamin pill and a dime.**

The small dimensions of the balloon device allow clinicians to retrieve samples quickly and easily without sedation during an outpatient exam.

Source: Moinova HR et al., Sci. Transl. Med., Vol. 10, Issue 424, eaao5848 (2018). Reprinted with permission from AAAS.

In 2016 and 2018, the results of an NCI-funded phase 2 clinical trial conducted by researchers at the Huntsman Cancer Institute at the University of Utah showed that treating patients for 6 months with sulindac, a nonsteroidal anti-inflammatory drug (NSAID), and erlotinib (Tarceva), a targeted therapy that blocks the activity of a protein called epidermal growth factor receptor (EGFR), reduced the burden of polyps in the small intestine, colon, and rectum by about 70% compared with patients who were given a placebo. Read how Gregg from Utah benefited from the combination treatment tested in the NCI-funded clinical trial on page 21.

Previous NCI-supported research had shown that EGFR plays an important role in colon tumor formation and progression and that blocking the activity of this protein might be useful in preventing colorectal cancer in people at increased risk of the disease. Additional research is needed to determine whether the malignant potential of the polyps that were prevented with sulindac and erlotinib is similar to that of the polyps that were not prevented.

NCI is supporting research to address this question and to further investigate this and other chemopreventive approaches aimed at reducing the risk of gastrointestinal cancers in people at increased risk, including individuals with FAP.

### Preventing All HPV-Associated Cancers

Although three effective human papillomavirus (HPV) vaccines have been approved by the Food and Drug Administration to date, none provides protection against all 13 identified high-risk (i.e., cancer-causing) HPV types. To provide greater protection, an international team of researchers with NCI support recently developed a vaccine called RG1-VLP (also known as RGVax) that consists of virus-like particles (VLPs) made from proteins that form the outer shell of HPV type 16 (HPV16).

Specifically, the VLPs are composed of the protein HPV16 L1 into which a segment of the protein HPV16 L2 has been inserted. In preclinical studies, the vaccine protected against infection by more than 20 types of HPV, including all 13 high-risk types. A second-generation vaccine, which also has the potential to prevent all HPV-associated cancers, will be tested in clinical trials in early 2019.

## Opportunities for Greater Progress

Thanks to basic research, our understanding of how cancers develop continues to grow. This increasing knowledge, together with the availability of powerful new technologies, is affording new opportunities to improve and expand our ability to prevent cancer. In addition to developing new methods of cancer prevention, we must overcome the barriers to implementing established approaches, such as the use of approved cervical and colorectal cancer screening tests and preventive vaccines, particularly in populations where they historically have been underutilized. Areas of opportunity for additional progress are described below.

*Increasing knowledge, together with the availability of powerful new technologies, is affording new opportunities to prevent cancer.*

### Understanding the Biology of Precancerous Lesions and their Progression to Cancer

Fully understanding the events that underlie the development of precancerous tissue changes and drive the transition to malignant disease will provide new opportunities for cancer prevention. This knowledge will also lead to the identification of molecular markers that will be useful in cancer risk assessment and early detection.

Toward this end, NCI has announced its intention to fund Pre-Cancer Atlas Research Centers as part of the Human Tumor Atlas Network, which was established under the Cancer Moonshot℠. These research centers will systematically collect, catalogue, and comprehensively analyze large numbers of precancerous lesions and early cancers, including their microenvironments, that have developed at specific organ sites.

## Identifying Risk Factors for Cancer

Identifying genetic and environmental risk factors for cancer and understanding how genes and the environment interact to influence cancer risk will enable the development of new approaches to prevent cancer. This knowledge will also lead to more precise assessments of cancer risk, allowing people at increased risk of cancer to receive the most appropriate medical care to manage their risk.

### Updating NCI's Breast Cancer Risk Assessment Tool for Hispanic Women

NCI's Breast Cancer Risk Assessment Tool (BCRAT) was recently updated to provide more accurate estimates of breast cancer risk for Hispanic women. This interactive tool, which was developed by researchers at NCI and the National Surgical Adjuvant Breast and Bowel Project, a former NCI clinical trials research cooperative group, provides estimates of a woman's risk of breast cancer over the next 5 years and during her lifetime.

The original BCRAT was based on data from white women and was less accurate in predicting risk for women of other races and ethnicities. For example, research had shown that the BCRAT substantially underestimated breast cancer risk for Hispanic women and that their risk of the disease is significantly influenced by their country of birth.

Therefore, NCI researchers used data on Hispanic women from the San Francisco Bay Area Breast Cancer Study, a multiethnic case–control study, and Hispanic breast cancer incidence and mortality data from the California Cancer Registry and NCI's Surveillance, Epidemiology, and End Results (SEER) Program to develop a breast cancer risk assessment model for Hispanic women that takes country of birth into account.

In 2017, this model was incorporated into the BCRAT. Similar updates had previously been made to improve the accuracy of the BCRAT for African American and Asian American women. Additional updates to the BCRAT will be made as new data and research become available.

More research in this area is needed, and several NCI programs support and pursue this type of research, which includes the development and validation of tools that can be used to assess risk at various stages of a person's life, within population subgroups, and across the general population

## Developing New Approaches to Cancer Prevention

It has been estimated that 30%–50% of cancers that occur today could be prevented by not smoking cigarettes, maintaining a healthy body weight, reducing exposures to environmental risk factors, and receiving recommended screenings and vaccinations. To reduce the incidence of these cancers, we must find innovative ways to help people change their behaviors and make healthy lifestyle choices.

*An estimated 30%–50% of cancers that occur today could be prevented.*

Additional research is also needed to address the 50%–70% of cancers that are not currently preventable. NCI supports a broad portfolio of research to increase our understanding of their underlying biology, develop new drugs or repurpose existing drugs for cancer chemoprevention, and develop new cancer prevention vaccines.

## Kristin—Florida

Breast cancer survivor

# Detecting and Diagnosing Cancer

The early detection and diagnosis of cancer usually increases the chances of successful treatment. In addition, treatments for early cancer are often less complex and less expensive than treatments for more-advanced disease, sparing patients and their families greater hardship. However, too many cancers are still diagnosed at late stages, when effective treatment and long-term survival may not be possible.

Another promise of early detection is the identification of precancerous tissue abnormalities that are destined to become life-threatening cancers, providing an opportunity for even earlier intervention to prevent cancer from developing altogether. Similarly, the ability to accurately identify precancerous tissue abnormalities and early cancers that will not progress to potentially fatal malignancies would also be beneficial, potentially sparing many patients and their families the physical and financial harms of unnecessary treatment.

As has been true for many years, NCI continues to support a broad portfolio of research aimed at improving the early detection and diagnosis of cancer and its precursors. Two major goals of this research are increasing the dissemination of proven methods of detection and diagnosis and developing new and improved methods that are more accurate and of greater value clinically than those available today. Another goal is to produce technologies and tests that are efficient and cost-effective and that can be used in all resource

## Detecting Cancer Early in Women with Dense Breasts

When Kristin learned she had breast cancer, her heart sank with the idea that her number was up. "Bingo. It's my turn," she thought.

After 20 years of work at the Mayo Clinic and as the widow of a Mayo researcher, Kristin was no stranger to cancer and disease—from both the research and clinical sides. Her own annual physical exams and mammograms at Mayo had always come up clean.

Things changed in August 2017, when a Mayo doctor invited her to participate in a research study of a new FDA-approved technology called LumaGEM, which uses a small amount of a radioactive chemical to detect breast cancer.

Developed with support from NCI's Small Business Innovation Research program, this new technology, which is a type of molecular breast imaging (MBI), is potentially promising for women with dense breasts whose mammograms are very difficult to read.

Kristin agreed to join the study, undergoing both routine mammograms and MBI. Although Kristin's mammograms continued to show no abnormality, her MBI scan revealed a mass that was confirmed by a biopsy to be an aggressive stage I breast cancer, which was removed surgically.

Kristin, who is undergoing additional treatment, reflected, "Were I not a research subject in that study, I don't know where I'd be today. This technology, I'm convinced, saved my life."

**40%–50%**

**OF U.S. WOMEN AGE 40–74**

**HAVE DENSE BREASTS**

Source: Sprague BL et al. J Natl Cancer Inst. 2014 Sep 12;106(10)

settings. Ultimately, this work should increase the number of cancers for which we have effective screening tests.

**Vision**

*Fewer people will suffer and die from cancer because we can detect and diagnose its precursors or the disease itself at the earliest possible stage.*

**Approach**

- *Expand the implementation of proven cancer screening tests.*
- *Improve current methods of detecting cancer and its precursors and develop new methods that are applicable to all cancer types.*
- *Identify and validate new biological molecules, or biomarkers, that can be used in the early detection and diagnosis of cancer and its precursors.*

## Progress in Detecting and Diagnosing Cancer

NCI funding has contributed to many major advances in cancer detection and diagnosis. For example, NCI supported research and consensus development conferences that established the effectiveness of screening mammography in detecting early breast cancer and that provided recommendations for mammography's use in routine clinical practice. In addition, NCI sponsored the ASCUS-LSIL Triage Study (ALTS), which, in 2003, led to the first Food and Drug Administration (FDA) approval of a human papillomavirus (HPV) test for cervical cancer screening.

Moreover, NCI sponsored large randomized clinical trials that demonstrated the effectiveness of two colorectal cancer screening tests (fecal occult blood test and flexible sigmoidoscopy) and of lung cancer screening with low-dose helical computed tomography in reducing mortality from colorectal cancer and lung cancer, respectively.

Examples of recent NCI-funded accomplishments in cancer detection and diagnosis are described below.

### Refining the Liquid Biopsy

The conclusive identification of circulating tumor cells in the blood of patients with cancer more than 60 years ago forecasted the development of the liquid biopsy. In this procedure, cancer cells or their components, such as DNA, can be detected through minimally invasive means in samples of blood or other bodily fluids. Advances in biomedical technology are now bringing the promise of the liquid biopsy for early cancer detection closer to the clinic.

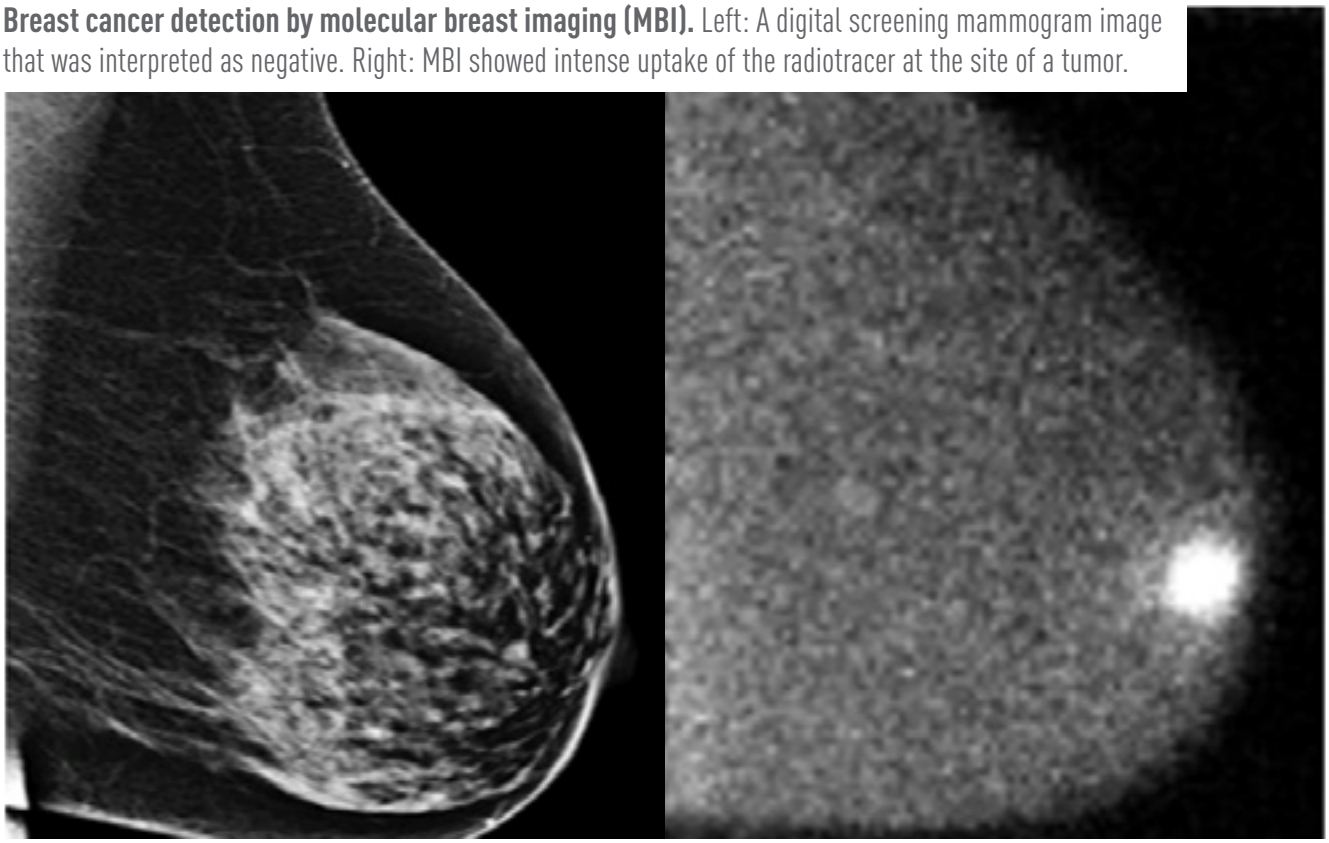
In 2018, a consortium of international and NCI-supported researchers and their colleagues reported the development of CancerSEEK, a blood test that measures the levels of 8 proteins and the presence of mutations in 16 cancer-related genes to detect early-stage cancers. In a retrospective analysis, when this test was applied to blood samples from 1,005 patients with 8 different types of nonmetastatic cancer, the presence of cancer was correctly identified 70% of the time. For five of the eight cancer types for which no screening tests are currently available (ovary, liver, stomach, pancreas, and esophagus), the sensitivity of detecting cancer ranged from 69% (esophageal cancer) to 98% (ovarian cancer).

NCI is supporting research to develop additional liquid biopsy tests for the early detection of cancer. Because all cancer screening tests have both benefits and harms (e.g., false-positive and false-negative test results), it will be critical to determine in prospective studies that the benefits of any test greatly outweigh the potential harms before it is introduced clinically.

### Improving Prostate Cancer Diagnosis

The routine collection of prostate tissue through the rectum (prostate biopsy) has led to the increased detection of low-grade cancers, which may not need treatment, and an increase in biopsy-related, potentially life-threatening bacterial infections. Reducing the biopsy rate for men who ultimately prove to have benign conditions or low-grade cancer would therefore be desirable.

**Breast cancer detection by molecular breast imaging (MBI).** Left: A digital screening mammogram image that was interpreted as negative. Right: MBI showed intense uptake of the radiotracer at the site of a tumor.



Credit: Reprinted with permission from AJR Am J Roentgenol ©2018.

In 2018, NCI intramural and NCI-funded extramural researchers reported that a risk prediction model based on multiparametric magnetic resonance imaging (mpMRI) of the prostate, in which specific characteristics of prostate tissue are highlighted to distinguish between healthy and unhealthy tissue, combined with prostate biopsies guided by standard MRI and transrectal ultrasound imaging could reduce the number of unnecessary biopsies by more than a third while still detecting nearly 90% of clinically significant cancers (i.e., those that need treatment).

These researchers and other NCI-funded investigators are studying ways to further refine this approach and to identify biomarkers that can distinguish potentially lethal prostate cancers that need to be treated from low-risk cancers that may not need treatment.

*Researchers are studying ways to distinguish potentially lethal prostate cancers that need to be treated from low-risk cancers that may not need treatment.*

## Enhancing Cancer Detection in Dense Breasts

The ability of mammography to detect breast cancer in women with dense breasts, which have substantially more glandular and connective tissue than fatty tissue, is lower than that for women with predominantly fatty breasts. Therefore, new technology is needed to improve breast cancer detection in women with dense breasts.

In 2004, NCI's Small Business Innovation Research program began supporting the development of LumaGEM, a molecular breast imaging (MBI) technology that uses small amounts of the radioactive compound 99mTc-sestamibi, which localizes to tumors, to detect breast cancer in women with dense breasts. In 2016, researchers showed that LumaGEM, which has been approved by FDA as an adjunct to mammography, correctly identified 11 invasive tumors that had been missed by standard mammography in a retrospective study involving 1,696 women.

Read about how Kristin from Florida had her breast cancer detected by MBI on page 27. NCI continues to support other avenues of research to improve breast cancer detection in all women.

### Accelerating Cervical Cancer Control

A long-standing issue in reducing the incidence and mortality of cervical cancer is how to make effective cervical screening available in regions or countries that have limited health care resources. Another issue is how to avoid unnecessary follow-up procedures in screened women with precancerous cervical tissue abnormalities that have a low risk of progressing to cancer.

Although human papillomavirus (HPV) testing can sensitively detect precancerous cervical tissue, another "triage" step is needed to identify women with tissue abnormalities that have the highest risk of progressing to cancer. These women, who are infected with the highest-risk HPV types and/or have severely abnormal cervical cells, are usually referred for additional medical tests, including a close examination of the cervix (colposcopy) and, possibly, a biopsy.

To address these issues, a research group led by NCI intramural investigators developed an automated approach that combines HPV testing, HPV typing, and computer-interpreted cervical cell analysis for screening and triage. This approach should eventually be adaptable for widespread use, including in regions and countries that have limited access to expert medical services. The researchers are also investigating the inclusion of specific biomarkers in their triage protocol to further improve its performance.

## Opportunities for Greater Progress

Improvements in genomic, proteomic, and imaging technologies are presenting new opportunities for major progress in cancer detection and diagnosis. These advances have the potential to increase our ability to identify and characterize tumor cells and other biomarkers in bodily fluids and are enabling more precise imaging. Research areas poised for greater progress are described below.

*There is a critical need for additional biomarkers to optimize the care of patients with cancer and at-risk individuals.*

### Identifying and Validating Biomarkers for Early Cancer Detection and Diagnosis

Recent advances in identifying biomarkers have improved early cancer detection and diagnosis. However, there is a critical need for additional biomarkers to optimize the care of patients with cancer and at-risk individuals. NCI supports several programs to promote research in this area.

For example, the Consortium for Molecular Characterization of Screen-Detected Lesions, currently led by investigators at eight institutions, supports research on the molecular and cellular features of precancers and early cancers detected through screening tests. The goal of this program is to enable doctors to distinguish precancers or cancers that will not become life-threatening from aggressive cancers that need to be treated.

Another program is the Alliance of Glycobiologists for Detection of Cancer, which supports eight laboratories conducting research on the cancer-related changes in complex carbohydrates (sugars) in cells to identify and validate biomarkers for early cancer detection.

A third program is the Early Detection Research Network, a public–private partnership that provides infrastructure and resources vital to the discovery, development, and validation of cancer-related biomarkers. Accelerating research in

this area is a key part of our efforts to reduce the morbidity and mortality of cancer.

### Developing Cancer Imaging Technologies

Medical imaging, with traditional x-rays, ultrasound, MRI, computerized tomography (CT), and positron emission tomography (PET), plays a central role in the detection and diagnosis of cancer. Each of these methods, however, has limitations, and ongoing research is investigating ways to improve their utility or develop entirely new technologies for cancer detection.

*Ongoing research is investigating ways to develop entirely new technologies for cancer detection.*

One newer approach, called digital tomosynthesis, allows 3-dimensional images to be constructed from multiple x-rays taken at different angles. This approach is currently being evaluated in NCI's Tomosynthesis Mammographic Imaging Screening Trial (TMIST) for the early detection of breast cancer.

Other approaches under investigation for which additional resources will enable greater progress include combining current imaging methods with computerized image analysis (i.e., artificial intelligence/machine learning); the molecular imaging of cancer biomarkers; the use of nanoparticles to detect and image cancer cells; microwave imaging; and photoacoustic imaging, in which laser pulses are used to generate ultrasonic waves in tissues that can be converted into images.

## Adam—Missouri

Acute lymphoblastic leukemia survivor

# Treating Cancer

NCI's commitment to developing new cancer treatments for patients includes basic research to discover the mechanisms of cancer and new drug targets, preclinical research to investigate the anticancer effects of therapies that target these mechanisms, and clinical research to test new therapies in patients.

NCI provides critical research funding and infrastructure to support all of these areas. For example, the NCI Specialized Programs of Research Excellence (SPOREs) promote collaborative, interdisciplinary translational cancer research to move basic scientific findings into the clinic. NCI's National Clinical Trials Network (NCTN) provides robust infrastructure to NCI-funded treatment, screening, and diagnosis trials to improve the lives of patients with cancer.

Our nation's investment in cancer research has yielded important new tools and treatments for patients. For example, NCI-funded research contributed to the development of each of the 14 novel cancer drugs and biologic agents approved by the Food and Drug Administration (FDA) in 2017. Ongoing research is building on the advances that have been made in cancer treatment to further improve the outlook for both adults and children with cancer.

## Learning from Every Patient to Improve CAR T-Cell Therapies

An avid fire juggler, 19-year-old Adam is used to challenging himself. The diagnosis of acute lymphoblastic leukemia (ALL) in 2015, however, stands as the biggest challenge he has faced. He was relieved when standard treatments put his cancer into remission. But during winter break of his freshman year of college, a checkup revealed the cancer was back.

Just months prior to Adam's cancer recurrence, FDA approved the first CAR T-cell therapy for patients with ALL. It is an immunotherapy that attacks leukemia cells with a specific protein on their surface. Adam's doctors hoped he would be one of the first patients treated with this new therapy.

Adam was disappointed to learn that the FDA-approved therapy would not work for him as his leukemia did not express enough of the right protein. However, his cancer did have high levels of another protein that other CAR T-cell therapies target, and Adam enrolled on an NCI intramural clinical trial testing one of them. He received his CAR T-cells in May 2018.

Adam does not know if this experimental treatment will benefit him but is not hesitant about participating in a trial. As a physics major and patient with cancer, he understands the importance of research. After being diagnosed, he had decided, "A clinical trial was on my bucket list," he said. He expects researchers will learn from his cancer so that progress can happen faster.

THERE ARE

**MORE THAN 240**

**REGISTERED CAR T-CELL THERAPY TRIALS IN CLINICALTRIALS.GOV**

Source: Sadelain M. Cell. 2017 Dec 14;171(7):1471.

**Vision**

*All patients with cancer will have safe and effective treatments.*

**Approach**

- *Discover and develop new cancer treatments, including those that involve molecularly targeted therapies and immunotherapies, as well as combinations of treatments.*
- *Improve traditional cancer treatment approaches, including surgery, radiation therapy, and chemotherapy.*

## Progress in Treating Cancer

Advances in molecularly targeted therapies and immunotherapies have transformed the treatment landscape for patients. NCI-funded research has led to a better understanding of cancer biology, fueling the development of new classes of drugs and precision cancer medicines. Improvements in traditional treatment approaches supported by NCI—such as surgery, radiation therapy, and chemotherapy—have also benefited patients. Below are some recent accomplishments in cancer treatment that showcase the impact of NCI-funded research.

### Reducing the Use of Chemotherapy in Early-Stage Breast Cancer

Results from TAILORx, an NCI-sponsored clinical trial, showed that most women with a common type of early-stage breast cancer do not benefit from adjuvant chemotherapy. This groundbreaking discovery will save thousands of women from unnecessary treatment. About half of all cases of breast cancer diagnosed in the United States are hormone receptor-positive, HER2-negative and have not spread to the patient's lymph nodes. Women with this type of breast cancer are typically treated with surgery and radiation followed by hormone therapy and chemotherapy to help prevent recurrence. Prior to this trial, investigators suspected that the addition of chemotherapy only benefited a small percentage of these women, but it was not clear whether an FDA-approved genomic test could identify them.

*Results from TAILORx, an NCI-sponsored clinical trial, will save thousands of women from unnecessary treatment.*

TAILORx set out to determine whether the test, which measures the expression of 21 genes associated with the risk of breast cancer recurrence, could be used to determine the benefit of chemotherapy. The trial showed that up to 85% of patients had low or intermediate risk of recurrence based on the test and that chemotherapy did not benefit the vast majority of these women. The 15% of patients who have a high risk of recurrence do benefit from chemotherapy. However, there was a subset of younger women with an intermediate risk score who seemed to benefit from chemotherapy; therefore, more research is needed to understand how to better identify and treat these women.

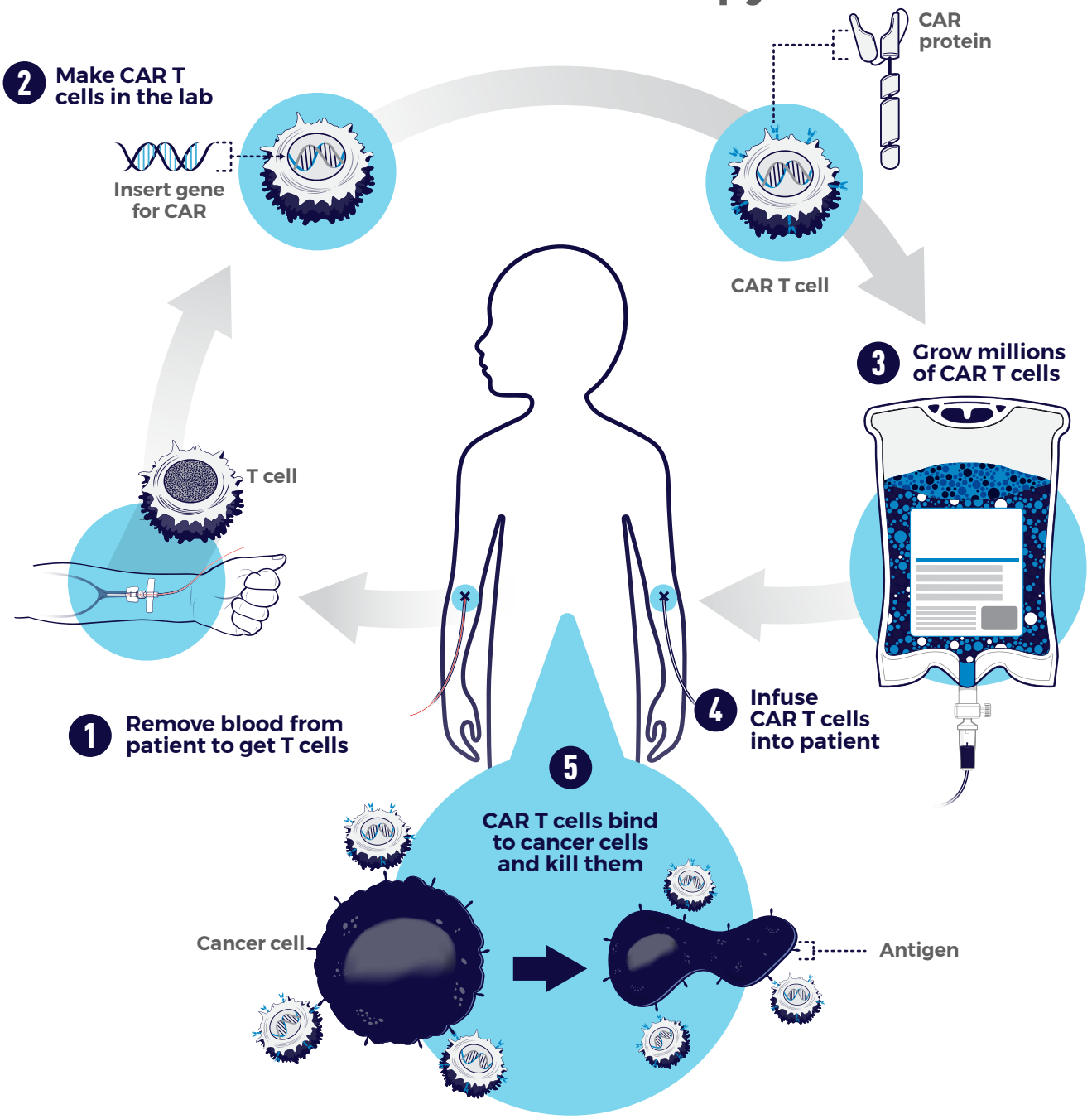
NCTN supported the TAILORx trial, which recruited more than 10,000 women from 1,182 sites across the United States. These practice-changing results mean most women with this type of early-stage breast cancer can be spared the short- and long-term adverse effects of chemotherapy.

### Bringing the First CAR T-Cell Therapies to Patients with Blood Cancers

Chimeric antigen receptor (CAR) T-cell therapies have resulted in remarkable benefits to patients with certain kinds of leukemia and lymphoma for whom other treatments have stopped working. Approved by FDA in 2017, CAR T-cell therapy is a class of immunotherapy in which a patient's own immune cells are genetically engineered to attack their cancer. NCI helped support the first clinical studies of a CAR T-cell therapy called tisagenlecleucel (Kymriah) for the treatment of children and young adults (up to age 25) with recurrent B-cell acute lymphoblastic leukemia and adults with certain types of large B-cell lymphoma.

Another CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), is also approved for the treatment of adults with certain types of large B-cell lymphoma. It was initially developed by investigators in the

# CAR T-Cell Therapy




CAR T-cell therapy is a type of treatment in which a patient's T cells are genetically engineered in the laboratory so they will bind to specific proteins (antigens) on cancer cells and kill them. **(1)** A patient's T cells are removed from their blood. Then, **(2)** the gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells in the laboratory. The gene encodes the engineered CAR protein that is expressed on the surface of the patient's T cells, creating a CAR T cell. **(3)** Millions of CAR T cells are grown in the laboratory. **(4)** They are then given to the patient by intravenous infusion. **(5)** The CAR T cells bind to antigens on the cancer cells and kill them.

NCI intramural research program who pioneered the development of CAR T-cell therapies and other types of cancer immunotherapies over the last 40 years.

*Investigators in the NCI intramural research program pioneered the development of CAR T-cell therapies and other cancer immunotherapies.*

Both FDA-approved therapies target a protein on cancer cells called CD19. Unfortunately, some patients initially respond to these treatments but then relapse, and other patients' cancers do not respond at all.

NCI-funded researchers are now working to understand the mechanisms of response and resistance to these therapies and to develop additional approaches for patients, including CAR T-cell therapies that target other proteins on cancer cells. Read one patient's perspective in the story about Adam from Missouri, who participated in a CAR T-cell clinical trial at NCI on page 33. Other research is focused on translating CAR T-cell therapy's success to patients with solid tumors.

## Providing Novel Targeted Therapies for Patients with Acute Myeloid Leukemia

After little progress in the development of new treatments for patients with acute myeloid leukemia (AML) in decades, FDA approved five new treatments for patients in 2017 and 2018. Three of these were first-in-class drugs that target different genetic mutations in the cancer. NCI-funded research played an important role in the discovery and development of all three drugs.

In collaboration with an industry partner, NCI supported the international phase 3 clinical trial of the drug midostaurin (Rydapt), which was approved for use in combination with chemotherapy for adults with mutations in a gene called *FLT3*. Midostaurin was the first targeted therapy shown to improve survival in this group of patients.

In addition, NCI-funded research identified mutations in the genes *IDH1* and *IDH2* in AML and studied their effects. These discoveries contributed to the development of two drugs: ivosidenib (Tibsovo) that targets mutant IDH1 proteins and enasidenib (Idhifa) that targets mutant IDH2 proteins. NCI also funded the first sequencing of the AML genome and has continued to support research to further understand the genomic drivers of AML and how to target them therapeutically.

## Developing a New Drug for Prostate Cancer

In 2018, FDA approved the drug apalutamide (Erleada) for patients with nonmetastatic prostate cancer whose tumors are resistant to standard hormone therapy and are at high risk of metastasis (spreading). This is the first drug proven to benefit this group of patients. Apalutamide blocks the activity of the androgen receptor, which prostate cancers rely on for continued growth.

NCI funded the discovery of apalutamide as well as preclinical research and phase 1 clinical development of the drug. Other NCI-funded research identified mechanisms of resistance to standard hormone therapy for prostate cancer, laying the scientific foundation for the future discovery and development of new drugs.

The prevention of prostate cancer metastasis represents an important unmet medical need; longer-term research will determine whether apalutamide, in addition to reducing the risk of metastasis, also improves patient survival.

## Improving Radiation Therapy for Patients with Brain Metastases

Brain metastases are a devastating complication of many cancers. For patients with brain metastases, surgery followed by whole-brain radiotherapy (WBRT) has been the standard treatment for decades. WBRT, while reducing the risk of recurrence and new metastases, can cause substantial cognitive harm and a deterioration in quality of life for patients.

In 2017, results of an NCI-funded phase 3 clinical trial conducted at 48 institutions in the United States and Canada showed that administering stereotactic radiosurgery (precisely targeted radiation) to the surgical site produced less cognitive dysfunction and equivalent survival compared with WBRT. This trial and other research suggest that stereotactic radiosurgery could be considered a standard of care after surgery for patients with brain metastases. NCI continues to fund research aimed at improving radiation therapy approaches.

## Opportunities for Greater Progress

More basic, translational, and clinical research is needed to develop additional safe and effective therapies for adults and children with cancer. To accelerate these efforts, NCI is also focused on activities such as building the National Cancer Data Ecosystem, which was recommended by the Cancer Moonshot℠ Blue Ribbon Panel, to leverage different types of data—from laboratory research to clinical care—to ensure we learn from every patient and inform the development of new cancer treatments and interventions. Enhancing the design and conduct of cancer clinical trials will also facilitate the testing of new cancer therapies. Investing in the following areas of opportunity will enable additional progress in cancer treatment.

*More basic, translational, and clinical research is needed to develop additional safe and effective therapies for adults and children with cancer.*

### Developing Precision Immunotherapies

Remarkable clinical progress has been made in cancer immunotherapy, including the availability of immune checkpoint inhibitors and CAR T-cell therapies. However, most patients with cancer do not currently benefit from these treatments, and they are associated with substantial toxicity in some individuals. Also, not enough is known about how these therapies work in diverse populations. Identifying why some patients' cancers respond and others' do not is a pressing need requiring additional resources, research, and collaboration.

One program aimed at addressing this need is the Partnership for Accelerating Cancer Therapies (PACT), launched in 2017 under the auspices of the Cancer Moonshot. PACT brings together federal agencies and 11 pharmaceutical companies to develop and standardize biomarkers to increase our understanding of how immunotherapies work in patients and to better predict patients' responses to them. These and other efforts are needed to refine the use of existing treatments and to discover new approaches, including combination strategies, so that more patients will benefit from immunotherapy.

### Improving Strategies to Overcome Drug Resistance

The development of drug resistance is a major cause of cancer treatment failure. Multiple factors within tumor cells themselves and external factors in the tumor microenvironment can cause resistance. NCI funding has increased our understanding of drug resistance and enabled the development of combination therapies that prevent or delay its occurrence. However, we need to learn much more at the basic biological level about the many ways cancer cells survive, grow, and spread despite treatment.

Research in this area is being accelerated by the Cancer Moonshot. More resources will help us to develop models that better predict patient outcomes; advance technologies for investigating single cells and interactions between cells in the tumor; and aggregate and analyze large and diverse datasets from laboratory studies, clinical trials, and patient outcomes in the real world. The goal of this research is the discovery of new drugs and drug combinations to prevent or overcome resistance in patients.

### Embracing the Potential of Big Data

Every day large amounts of data are generated from cancer research and clinical cancer care that create opportunities to develop more effective treatments. Data collected from patients with cancer include tumor sequences, pathology

reports, medical images, clinical characteristics, and details about treatments and outcomes. Multiply the data collected from a single patient by the hundreds of thousands of patients treated for cancer each year, and the result is a wealth of information that could hold the key to better therapies and improved outcomes.

To fully leverage the potential of this information, mechanisms are needed that allow data to be shared, aggregated, and analyzed in a secure manner. Aggregating and linking these data will enable identification of associations between molecular data and other patient data, including treatment response and outcomes.

To support this need, NCI has embarked on building a Cancer Research Data Commons (CRDC) that is serving the spectrum of cancer research. The technologies, standards, and processes established through the NCI CRDC will contribute to the National Cancer Data Ecosystem recommended by the Cancer Moonshot Blue Ribbon Panel. This ecosystem will engage the private sector, academia, and philanthropic organizations in collaborating to share their collective data, maximizing the usefulness of the data, and expediting discoveries by the research community.

## Discovering Novel Drug Discovery Approaches

Precision medicines for cancer provide new, more targeted approaches for cancer therapy. Most of these drugs interfere with abnormal proteins that cancer cells use to grow and survive. Large initiatives, such as The Cancer Genome Atlas, combined with the efforts of individual NCI-funded laboratories, have resulted in the discovery of many genes that drive cancer and potential drug targets, but relatively few small-molecule drugs have been developed to disable these targets. Many important targets have properties that make it difficult to develop effective drugs using current drug-design and development methods.

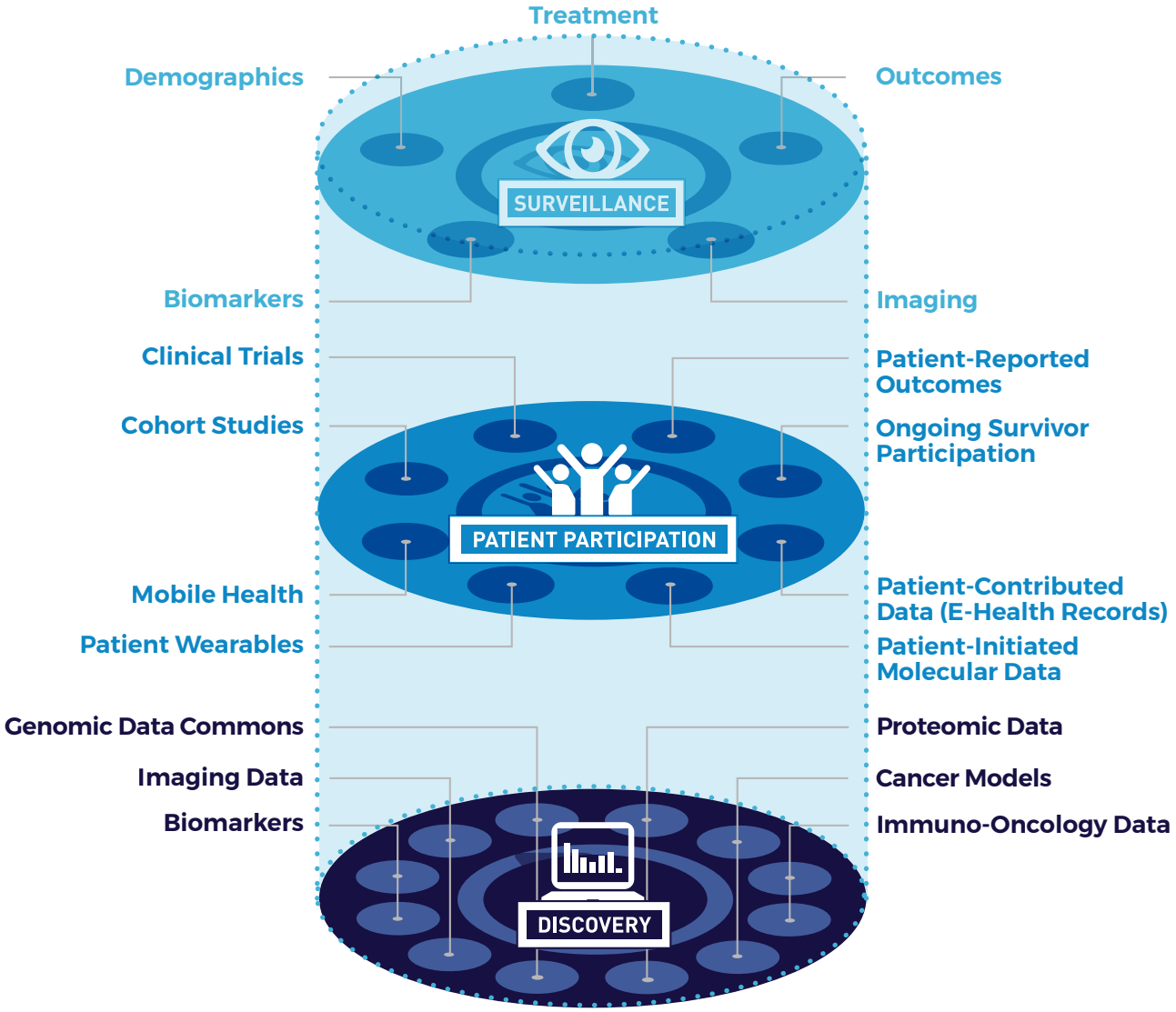
Additional research investments are needed to pursue novel approaches to these and other targets. For example, newer research is revealing a wealth of previously unrecognized therapeutic targets, such as noncoding RNAs (molecules that regulate the expression of genes) that are involved in cancer. Advances in technology, including nanotechnology-based drug delivery, also provide opportunities for expanding the cancer treatment armamentarium.

### Enhancing Cancer Clinical Trials

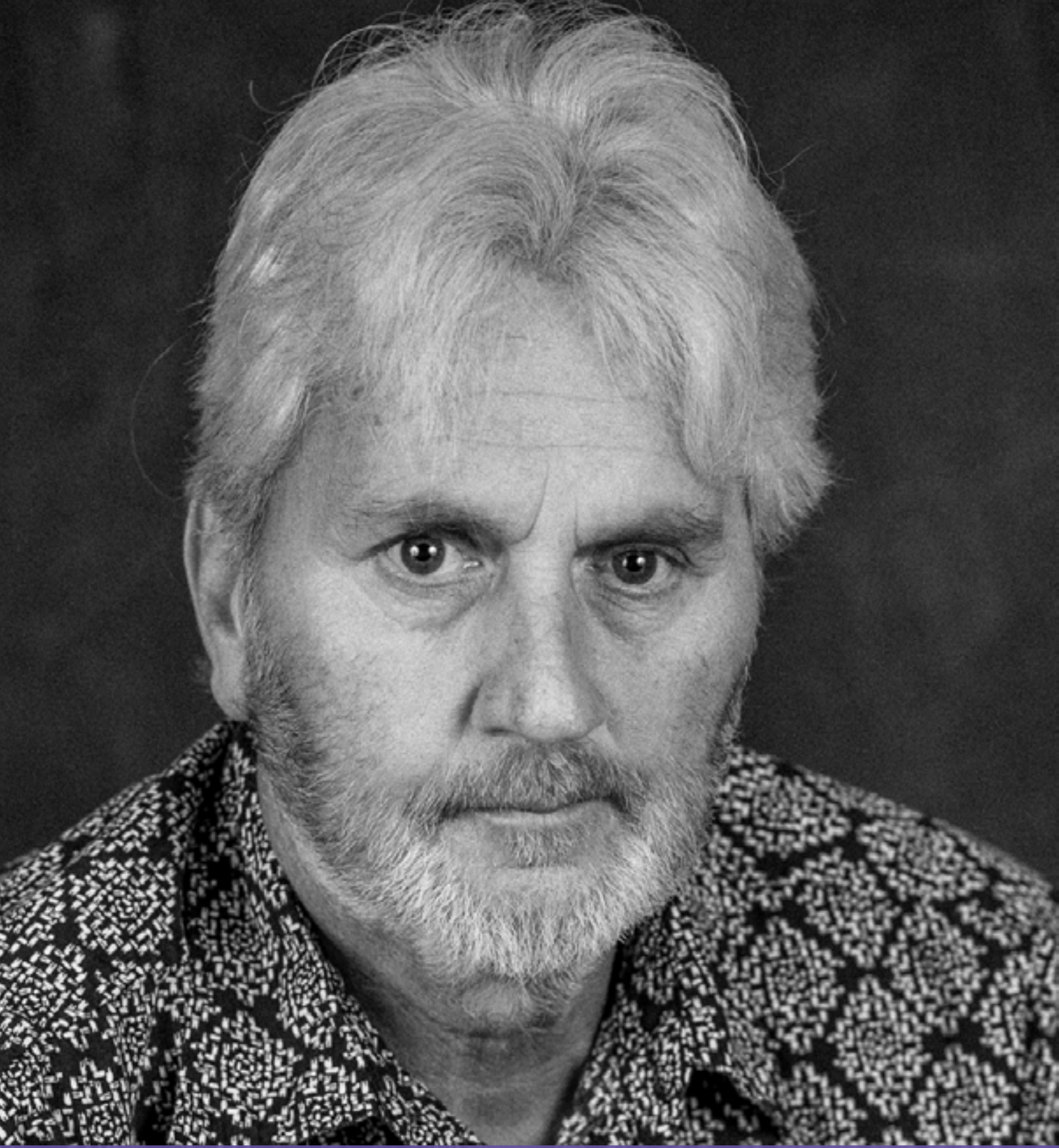
Clinical trials are a fundamental means by which progress in cancer treatment and prevention is made. However, the growing challenges involved in conducting clinical trials are hindering investigators' abilities to test the safety and effectiveness of new treatments. Some of the challenges include the rising costs of conducting trials, the increasing complexity of trials needed to reflect the molecular heterogeneity of cancer, and low patient accrual to trials. NCI efforts are aimed at addressing these challenges so that the way clinical trials are conducted will make them work better for patients and providers.

The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) and NCI-COG Pediatric MATCH trials are examples of NCI's leadership in addressing these challenges by supporting large-scale precision medicine trials with robust and diverse patient participation across the United States. Through our clinical trial networks and investigator-initiated studies, NCI leads additional efforts to support innovative trial design, support clinical trials that test novel ideas, and enroll patients in community settings.

# Integrating Cancer Research Data




To advance precision medicine in cancer care, a National Cancer Data Ecosystem is a necessity. This evidence-based knowledge system will facilitate the integration of data from research and clinical care. NCI is in a unique position to build the research data components of this ecosystem and to promote a culture of data sharing among all stakeholders. While there are many types of data currently available to researchers, such as those depicted in the figure, they must be harmonized and integrated to have the desired impact on cancer care. NCI can play a central role in aggregating and harmonizing research data from many existing cancer research studies and consortia, and the institute is creating an infrastructure, the Cancer Research Data Commons (CRDC), to support this goal. Comprised of repositories for diverse data types and tools for sharing and analysis, the CRDC will facilitate collaboration, team science, and discovery. As both the volume and types of data increase, NCI is expanding this infrastructure to include software tools for data analysis across repositories and contributing to the larger National Cancer Data Ecosystem that will support and learn from every patient with cancer. Over time, the goal is to incorporate the spectrum of NCI cancer research data into the CRDC, allowing researchers to develop new knowledge that will expedite discovery and advance cancer care.



## Tony—Tennessee

Rectal cancer survivor

# Advancing Public Health in Cancer

Cancer and the many issues associated with it have a significant impact on public health in the United States. Researchers are addressing them by studying cancer and its burden on a population-wide scale. NCI-funded research findings are used to protect the health of people and their communities and to inform the development and implementation of policies and programs to reduce the burden of cancer. NCI's investments in cancer control, population health, and survivorship are aimed at reducing cancer risk, incidence, and mortality and on improving the quality of life of cancer survivors and the general population.

Colorectal cancer screening is one example of a public health measure that has contributed to the decrease in cancer incidence and mortality rates. Wider dissemination could result in even greater improvements in public health, and NCI is supporting research toward this goal. NCI funds a wide range of studies to enhance the delivery of high-quality cancer care and to develop and implement new and proven interventions targeted at the individual, institutional, and population levels.

*NCI-funded research findings are used to protect the health of people and their communities.*

## Quitting Smoking after a Cancer Diagnosis

Tony chain-smoked during the 40-mile drive to the Vanderbilt-Ingram Cancer Center in May 2018. He had a feeling he had cancer. For a year and a half, he had lived with symptoms that were not diagnosed by his local doctors. When the pain became unbearable, he knew he needed help.

His worst fears were confirmed when he was told he had rectal cancer. "It was devastating," said Tony. It was also a "wake-up call" to quit his four-decade cigarette habit.

The NCI-funded tobacco cessation program at Vanderbilt gave him the tools he needed to quit successfully. Using nicotine patches curbs his urges, and keeping his hands busy helps replace the cigarettes that have occupied them most of his life.

Doctors told Tony that quitting will improve his chances of successful cancer treatment, which, in his case, includes chemotherapy and surgery. He noticed more immediate benefits, though. Within days of quitting, he could no longer hear the wheezing sounds coming from his lungs at night.

Tony's cancer diagnosis changed his outlook on life. "I realize now that every cigarette was taking time off my life. I want to see my grandkids grow up."


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

**Vision**

*All population groups will benefit from advances in cancer research.*

**Approach**

- *Support the development, implementation, and population-wide dissemination of new and improved interventions to reduce the risk of cancer.*
- *Make high-quality cancer care available to everyone in the United States.*
- *Ensure that cancer survivors have the highest possible quality of life.*

## Progress in Advancing Public Health in Cancer

NCI funds basic and applied research in the behavioral, social, and population sciences to develop or enhance interventions that help reduce the burden of cancer in the United States. As part of this effort, NCI collaborates with other federal agencies and organizations at the global, national, state, and local levels to share evidence-based interventions for cancer control. Recent accomplishments in this area are listed below.

### Tracking Treatment Trends, Costs, and Outcomes for Elderly Patients with Cancer

Public health professionals need reliable sources of data to inform their cancer control efforts and to improve cancer outcomes in the United States. To meet this need, NCI has made high-quality cancer incidence, mortality, and survivorship data available through its Surveillance, Epidemiology, and End Results (SEER) Program since 1973. These data are widely used by researchers and the public for describing and understanding cancer trends in the United States and for identifying emerging issues of importance to public health.

For example, NCI-supported researchers used data from the SEER–Medicare Linked Database to examine the trends, costs, and outcomes of cancer treatment for older Americans (age 65 and older) diagnosed with metastatic colon cancer from 2000 through 2009. The researchers found

*NCI has made high-quality cancer incidence, mortality, and survivorship data available through its Surveillance, Epidemiology, and End Results Program since 1973.*

that the percentage of patients older than age 75 who received three or more cancer therapies increased from 2%–53% during this period. They also found that the 1-year cost of treating these patients increased by 32%, but their median survival improved by only 1 month. In addition, many of the administered drugs are associated with substantial toxic side effects that may reduce a patient's remaining quality of life. This study is an example of the usefulness of SEER data in determining clinical care patterns and patient outcomes. Research like this is necessary to inform improvements in clinical practice.

### Reducing Tobacco Use among Patients with Cancer

Patients with cancer who quit smoking at the time of their diagnosis may reduce their risk of dying by up to 40%. Studies have also shown that smoking cessation can increase the effectiveness of cancer treatments and improve the body's ability to heal. Therefore, NCI continues to support research on ways to reduce tobacco use by patients with cancer in the United States and globally.

One ongoing NCI-funded clinical trial at the University of Pennsylvania and Northwestern University is evaluating the effectiveness of extended use of varenicline (Chantix) for 24 weeks compared with the standard 12 weeks of therapy. Preliminary findings from this study showed that varenicline can yield quit rates of about 40% in patients with cancer, which mirrors the rates reported in the general population. In addition, varenicline did not increase adverse psychiatric or cardiovascular side effects in these patients, and smoking cessation improved patients' cognitive function and mood over time. Furthermore, the

rate of varenicline adherence among patients with cancer was about equal to that seen in the general population and was strongly predictive of tobacco cessation.

To increase tobacco cessation among patients with cancer, NCI launched the Cancer Center Cessation Initiative in 2017. Under this initiative, 22 NCI-Designated Cancer Centers are integrating science-based smoking cessation treatment services into daily clinical care and are helping patients and physicians overcome barriers to cessation treatment services. Read about how cancer survivor Tony from Tennessee has benefited from one of these programs on page 41.

### Using Nicotine Metabolism Rates to Tailor Smoking Cessation Therapy

NCI-funded researchers and their colleagues identified a biomarker that doctors can use to categorize their patients who smoke into two groups: those who metabolize nicotine quickly and those who metabolize it at a slower rate. In a randomized controlled clinical trial conducted at four sites in the United States and Canada, the researchers showed that the drug varenicline (Chantix) worked better than the nicotine patch for fast metabolizers, whereas both medications worked equally well for slow metabolizers. However, the slow metabolizers who took varenicline experienced a significant increase in adverse side effects, indicating that the nicotine patch was a better treatment option for them. This study demonstrates how doctors can use "precision prevention" approaches to select a cessation therapy that is likely to be most effective for their individual patients.

## Reducing the Risk of Oral Cavity and Oropharyngeal Cancers

Recent studies have shown that approximately 70% of cancers of the oropharynx (the part of the throat at the back of the mouth) may be linked to human papillomavirus (HPV) infection. It has been estimated that more than 16,000 cases of this cancer are diagnosed annually in the United States.

To determine the impact of HPV vaccination on oral HPV infections, NCI intramural researchers and their collaborators at Ohio State University and MD Anderson Cancer Center studied 2,627 men and women aged 18–33 who participated in the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES), 2011 to 2014. This group included individuals who had received at least one dose of the HPV vaccine 4 years earlier on average and unvaccinated individuals.

The researchers found that the rate of oral HPV infections was 88% lower in vaccinated versus unvaccinated individuals. Because HPV vaccination rates in this country are low, the estimated population-wide effect in reducing oral HPV infections was only 17%. Increasing vaccination rates would substantially lower the rate of oral HPV infections and the incidence of oropharyngeal and other HPV-associated cancers.

*Increasing vaccination rates would substantially lower the incidence of HPV-associated cancers.*

## Improving Colorectal Cancer Screening Rates with a Digital App

Colorectal cancer (CRC) remains the second leading cause of cancer death in the United States. Screening tests can prevent CRC by finding precancerous polyps that can be removed before they progress to cancer. Screening can also detect CRC at early stages when it is treatable and has a high cure rate. Despite these benefits, more than one-third of eligible adults in the United States (those age 50–75) do not get screened.

In an effort to improve the rate of CRC screening, NCI-funded researchers developed and tested an interactive computer app and found that it successfully encouraged patients to get screened. In a clinical trial involving 450 patients, about half of those who were randomly assigned to use the Mobile Patient Technology for Health-CRC (mPATH-CRC) app self-ordered a CRC screening test. Approximately one-third of the mPATH-CRC user group followed through with the screening

test, a two-fold increase over individuals in the control group, who watched videos about diet and exercise but did not receive the option to self-order a screening test.

## Opportunities for Greater Progress

Cancer has a major impact on public health in the United States, and its effects will continue to grow as the population ages. Despite the advances we have made to date, too many people still die from cancer and too many survivors continue to suffer from the aftereffects of cancer and its treatment. This burden is of particular concern for pediatric cancer survivors, who often suffer from severe or chronic health conditions into adulthood.

In addition, the financial costs of cancer on individuals, their families, and society are increasing rapidly. These facts underscore the need for additional research and more discoveries that will benefit everyone. Additional investments in the areas of opportunity described below will enable further progress.

### Improving Cancer Prevention, Diagnosis, and Treatment in Rural America

People who live in rural communities comprise approximately one-sixth of the US population. Compared with people living in urban areas, those residing in rural areas experience a lower incidence of cancer but a higher cancer mortality rate. In addition, the decreases in cancer mortality rates observed in recent years have been smaller in rural areas than in urban areas. Specifically, from 2006 through 2015, cancer deaths declined by 10% in rural areas, whereas, in urban areas, they declined by 16%.

These differences can be attributed to many factors, including higher rates of poverty and modifiable risk factors, such as cigarette smoking and an unhealthy body weight, in rural populations, as well as reduced access to high-quality health care due to transportation barriers, limited availability of specialist physicians and clinical trials, and lack of cancer support services.

Increased funding to develop and implement effective programs for rural cancer control are greatly needed. To lay the groundwork, NCI is supporting implementation research conducted by NCI-Designated Cancer Centers geared toward improving cancer control in rural areas. In addition, NCI is collaborating with other government agencies and other organizations to share information and ideas to address this area of unmet need.

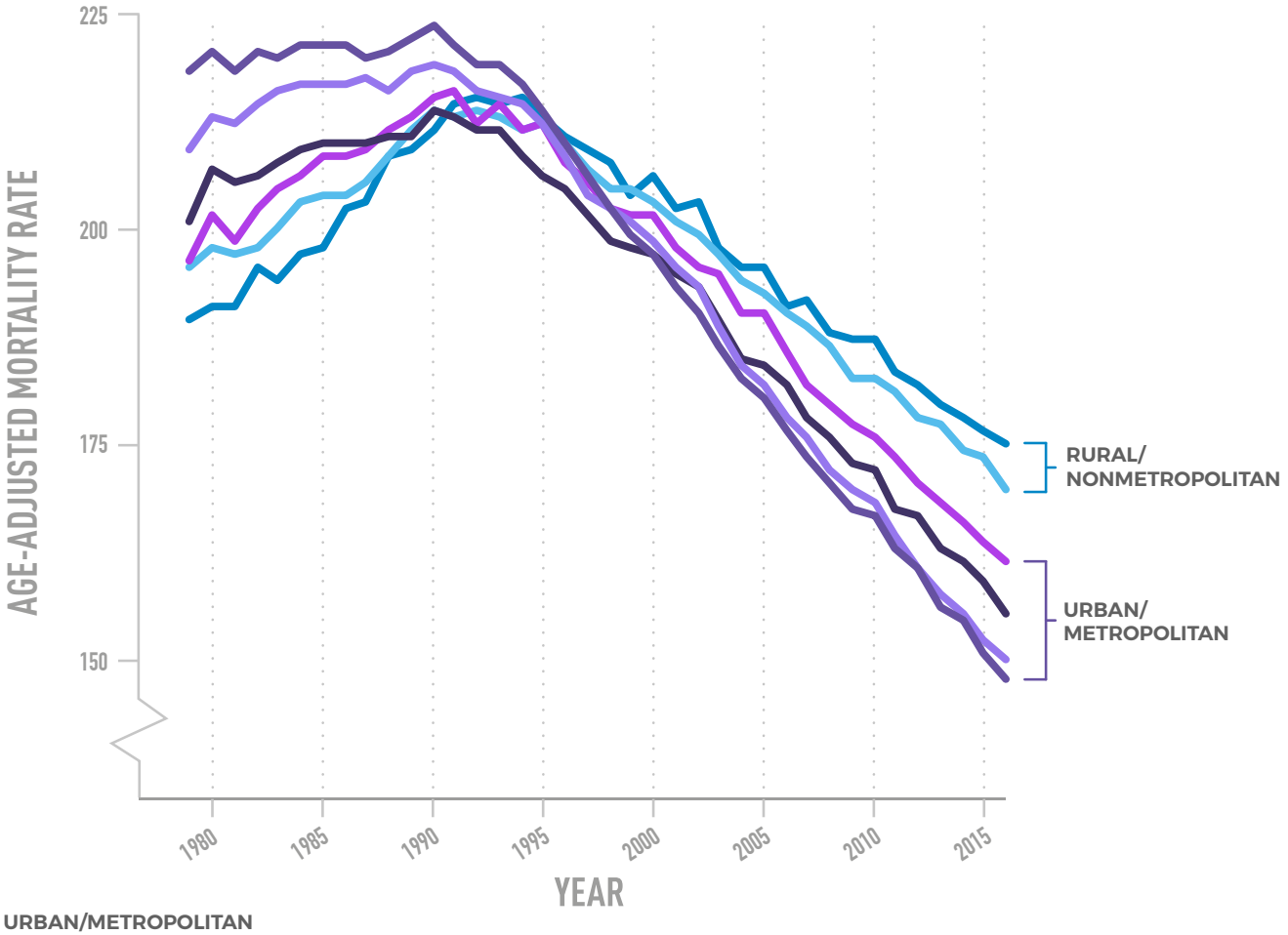
*Effective programs for rural cancer control are greatly needed.*

### Studying Biological and Nonbiological Factors to Reduce Cancer Disparities

Although progress has been made in reducing the overall burden of cancer in the United States, certain groups of people suffer disproportionately from higher incidence and mortality rates for some cancers than the general population. For example, African American men are more likely than white men to develop prostate cancer in their lifetimes, and they are more likely to be diagnosed with aggressive disease. As a result, their risk of dying from prostate cancer is twice that of white men.

To address this cancer disparity, NCI, the National Institute on Minority Health and Health Disparities (also part of NIH), and a nonprofit foundation are supporting the RESPOND study (Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress), which was launched in 2018.

# Deaths from Cancer: Rural vs. Urban Populations




**URBAN/METROPOLITAN**

**CENTRAL**
Counties in MSAs* with populations of at least 1 million

**FRINGE**
Counties in MSAs with populations of 1 million or more that did not qualify as central

**MEDIUM**
Counties in MSAs with populations of 250,000 but less than 1 million

**SMALL**
Counties in MSAs with populations of less than 250,000

*MSA=Metropolitan Statistical Area

**RURAL/NONMETROPOLITAN**

**MICROPOLITAN**
Contains an urban core with a population of at least 10,000 but less than 50,000

**NONMICROPOLITAN**
Contains an urban population of less than 10,000 or is a single county

Mortality Data Sources: The Compressed Mortality File is produced by the National Center for Health Statistics (NCHS) Office of Analysis and Epidemiology (OAE) at the Centers for Disease Control and Prevention (CDC). Mortality information is collected by state registries and provided to the National Vital Statistics System. Underlying cause of death and demographic descriptors are indicated on the death certificates.

Rural residents, who comprise 14%–19% of the U.S. population, have had higher cancer death rates than urban residents in recent years. This trend, the opposite of what was seen before 1995, has been attributed to numerous challenges faced by rural populations compared with urban populations, including higher poverty rates, less access to health services, lower educational attainment, and higher rates of behavioral risk factors, such as smoking.

RESPOND is the largest coordinated research study investigating environmental and genetic factors related to the aggressiveness of prostate cancer in African American men. The results of this study and other research focused on cancer disparities supported by NCI should inform the development of better ways to prevent and treat cancers that disproportionately impact some populations.

## Optimizing Symptom Management for Cancer Survivors

Cancer survivors frequently experience many short- and long-term adverse effects from cancer and its treatment. Common conditions and symptoms associated with cancer therapy include nausea and vomiting, peripheral neuropathy (nerve damage), cardiotoxicity (heart damage), hearing loss, cognitive challenges, depression, pain, and prolonged fatigue. Other problems can include an increased risk of developing another cancer (a second primary cancer), loss of fertility, financial difficulties due to the high cost of cancer treatment, difficulties with employment, and increased insurance costs. Some of the adverse effects of cancer treatment may reduce a patient's willingness to adhere to recommended therapies.

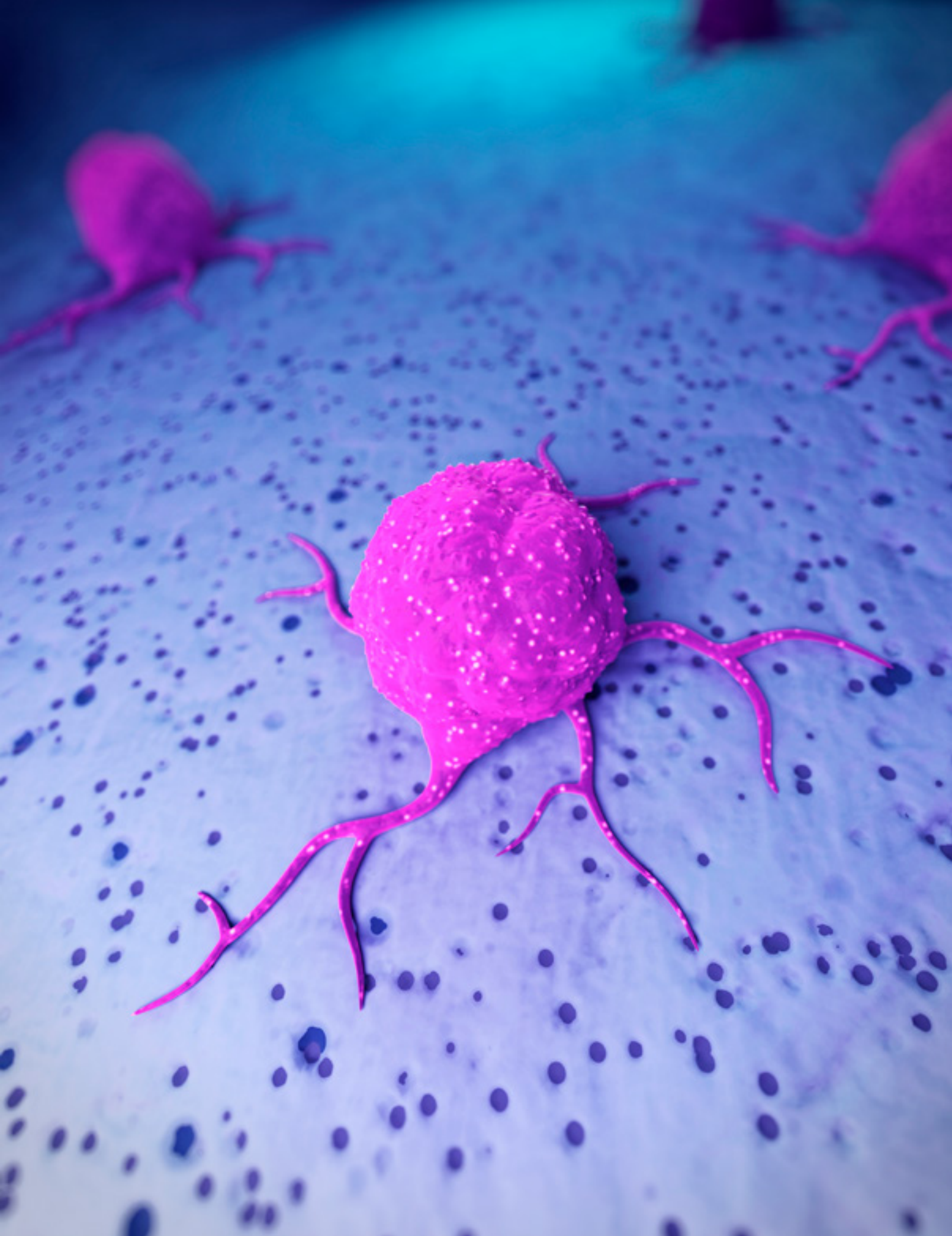
The Cancer Moonshot℠ is currently supporting research on patient-reported symptoms to improve patients' quality of life and adherence to treatment. This research focuses on standardizing patient-reported symptoms, assessing how patients tolerate different cancer treatments, and improving how doctors manage patient symptoms during treatment. With more research in this area, we will develop a better understanding of how to improve the quality of life of cancer survivors.

*With more research, we will develop a better understanding of how to improve the quality of life of cancer survivors.*

## Monitoring Survivors' Recurrent and Second Cancers

Two of the most difficult circumstances following cancer treatment are disease recurrence and the diagnosis of a second cancer. Nearly one in five cancers diagnosed today occurs in a person with a previous diagnosis of cancer. These second cancers are a leading cause of morbidity and mortality among survivors. Post-treatment surveillance guidelines provide the best evidence for monitoring patients after cancer therapy, but they are not available for all cancer types or may not be based on the latest evidence.

NCI supports research on more precise screening and diagnostic tests for the earlier detection of recurrent and second cancers and on survivorship care planning, including adherence to post-treatment surveillance and other follow-up care. Research into the causes, prevention, detection, and treatment of recurrent disease and second cancers will help improve how doctors manage the care of survivors and provide further insights into cancer biology.



## Victoria—North Carolina

Associate Professor, UNC Lineberger Comprehensive Cancer Center

# Strengthening the Cancer Research Enterprise

The National Cancer Act of 1971 authorized NCI to coordinate cancer research across the United States. In the ensuing decades, NCI has built and supported an infrastructure, comprising people working in science and the places at which they work, that has become known as the cancer research enterprise. Training the next generation of cancer researchers, coordinating the research and clinical trials infrastructure, and providing shared resources are some of the ways NCI strengthens the cancer research enterprise. Through basic and applied research, the efforts of researchers and organizations continue to advance progress in cancer prevention, detection, and treatment to produce better outcomes for patients and for those at risk for cancer.

## Supporting Scientists at Every Career Stage

NCI supports a talented scientific workforce over the course of their careers—from students just starting to explore a career path to established investigators. The goal of this support is to foster a community of scientists from diverse backgrounds that strengthens cancer research and its translation to patients.

## Extending Support for Early-Stage Investigators

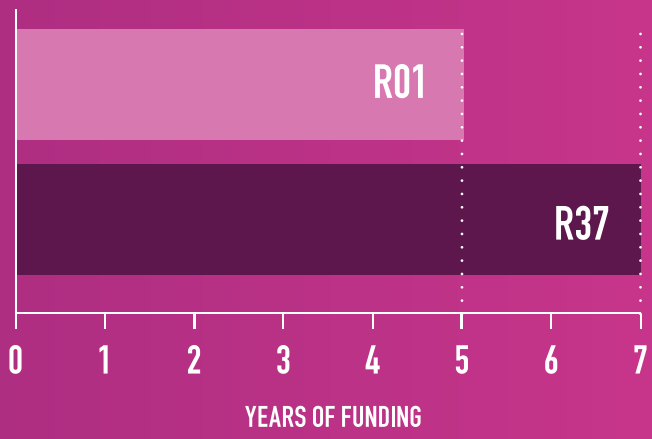
Victoria Bae-Jump, M.D., Ph.D., credits her father, a pediatrician, for her foray into medicine and notes how encouragement from mentors during her formative research years helped her persevere. While building her laboratory, she worked hard to balance her time seeing patients in the clinic and writing numerous grant applications to support her research, all while parenting a growing family that includes twins.

She received training and career development grants from NCI that allowed her to focus on her research in addition to her clinical responsibilities. She appreciates that NCI provides funding opportunities to scientists at every career level, including early-stage investigators like her.

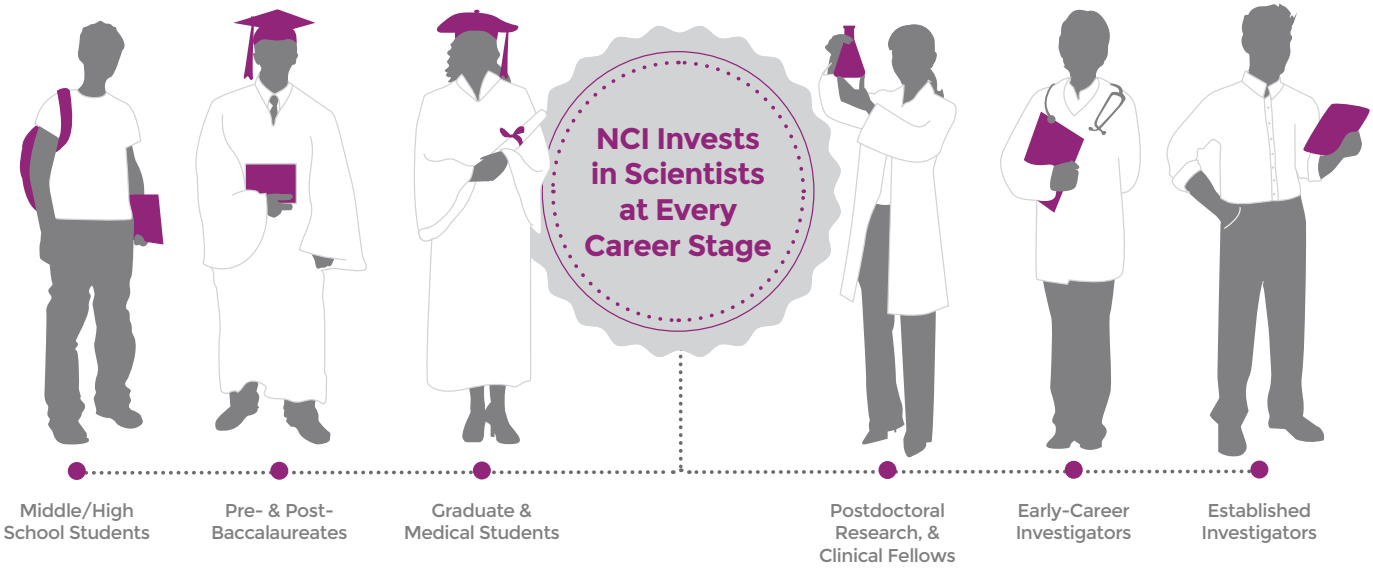
Victoria reached a milestone in 2018, when she received her 5-year R01 grant from NCI to study the metabolic and molecular differences of endometrial tumors in obese and nonobese women. "The R01 gives you the feeling that you've finally made it," Victoria reflected. "It gives credibility."

She was thrilled further to hear that NCI converted her R01 grant into an R37 award, providing her the possibility of 2 additional years of funding, for a total of 7 years of support. "Sometimes just doing your research is what you need to do, rather than writing grant applications all the time," Victoria said. "The 2 extra years of funding," she added, "will allow me and my laboratory more time and resources to identify better ways to prevent and treat patients with endometrial cancer."

### MERIT: R37 AWARD



# Supporting the Cancer Research Workforce




A large portion of NCI's budget funds investigator-initiated research proposals that have undergone a rigorous peer review process. This funding provides support to highly skilled scientists, working in their areas of expertise, who have submitted encouraging preliminary data. Much of the progress we have made against cancer to date had its origins in investigator-inititated research.

## Training the Next Generation of Cancer Researchers

NCI helps prepare individuals for careers in cancer research through training, career development, and mentored research opportunities for younger scientists on NCI's campuses in Maryland and across the nation. In 2017, NCI trained more than 3,800 scholars and early-career scientists, ranging from high school students through postdoctoral students and fellowship recipients. Specific examples of support included the following programs:

- Since 1992, the Cancer Prevention Fellowship Program has trained postdoctoral fellows in the principles and practice of cancer prevention and control. Thirty-seven fellows participated in the program in 2017. Most program alumni have continued careers in cancer research.
- In 2017, NCI funded 665 trainees and investigators through the Continuing Umbrella of Research Experiences (CURE) program, which promotes diversity in the cancer research workforce by supporting underrepresented minorities. Since its inception in 2001, more than 4,000 students and investigators have benefited from CURE training and support.
- In 2017, the Partnerships to Advance Cancer Health Equity (PACHE) program, in which institutions that provide care to underserved populations affected by cancer disparities are paired with NCI-Designated Cancer Centers, helped nearly 750 trainees from diverse backgrounds conduct cancer research.

## Increasing Investment in Early-Career Investigators

Scientists embarking on independent careers may face challenges that impede their success and make it difficult to remain in research. To address this issue, NCI supports early-career investigators in many ways. For example, in 2018, NCI retooled the Method to Extend Research in Time (MERIT) award to provide up to 7 years of support for early-stage investigators with their first R01 grant, compared with 5 years of support for the traditional R01 grant. The MERIT award offers

investigators more stability to launch their careers, enables creativity and innovation, and provides a longer amount of time during which they can apply to renew their current grant and/or apply for new grants. Read about the impact this additional support will have on early-stage investigator Victoria Bae-Jump from North Carolina on page 49.

NCI is supporting more early-stage investigators than in the past with the goal of ensuring a robust pipeline of future cancer research leaders.

*NCI is supporting more early-stage investigators than in the past with the goal of ensuring a robust pipeline of future cancer research leaders.*

### Supporting Established Investigators

NCI continues to support scientists who have an established record of productivity through a variety of funding mechanisms, such as investigator-initiated research project grants, and collaborative funding mechanisms, such as Specialized Programs of Research Excellence (SPORE) grants and Cancer Moonshot funding. Most awards made from NCI's research project grant pool are awarded to established investigators following a rigorous peer-review process.

## Providing Infrastructure and Resources for Cancer Research and Patient Care

NCI supports the cancer research community through an infrastructure that connects investigators in academia, community settings, and the private sector. By ensuring that scientists are equipped to test ideas and make discoveries that advance cancer research and clinical care, NCI puts patients at the forefront.

This infrastructure has been key to enabling rapid accrual to the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial, in which patients are assigned to treatment based on the genetic changes found in their tumors through genomic sequencing and other tests. In fiscal year 2017, approximately 30,000 new patients enrolled in NCI-sponsored or -supported clinical trials. Key infrastructure components include research centers, networks, and programs.

### Supporting Cancer Researchers and Centers around the United States

NCI-Designated Cancer Centers serve as a foundation of our nation's cancer enterprise. There are 70 cancer centers in 36 states and the District of Columbia, many of which are affiliated with university medical centers, enabling scientific research and clinical practice to better inform each other. At any given time, hundreds of research studies are underway at the cancer centers, from basic research to clinical studies. Approximately 250,000 patients receive their cancer diagnosis at an NCI-Designated Cancer Center each year.

**NCI CANCER CENTERS DIAGNOSE**

**250,000 CANCER CASES**

**EACH YEAR**

*NCI-Designated Cancer Centers serve as a foundation of our nation's cancer enterprise.*

**Stephenson Cancer Center, Oklahoma.** NCI's 70th Designated Cancer Center

## Enrolling Patients with Cancer in Clinical Trials across the United States

NCI has a long history of supporting clinical trials, many of which have led to changes in standard medical practice.

NCI's National Clinical Trials Network (NCTN), which is comprised of six clinical research groups (five in the United States and one in Canada), provides access to clinical trials at 2,400 sites across North America. The NCI Community Oncology Research Program (NCORP) brings cancer clinical trials to the communities where patients live, making it easier for them to access cancer care. The program includes 34 community sites and 12 minority/underserved community sites that are associated with 930 public hospitals, physician practices, academic medical centers, and other groups across the nation.

Through NCTN, NCORP, and the NCI-Designated Cancer Centers, NCI is increasing support for clinical trials and working to boost patient and physician participation. For example, approximately 44% of NCI-MATCH trial participants enrolled through NCORP.

*NCI is increasing support for clinical trials and working to boost patient and physician participation.*

## Making Cancer Research Resources Available

NCI develops and maintains resources—such as databases, specimen repositories, and tools—that are available through a portal on NCI's website. Just one example of an NCI resource is the Surveillance, Epidemiology, and End Results (SEER) program, an authoritative source for cancer statistics in the United States, covering nearly 35% of the US population. This coverage includes more than 49% of American Indians/Alaska Natives, 57% of Asians, and 68% of Native Hawaiian/Pacific Islanders.

Researchers and policy makers use SEER data to understand and monitor changes in cancer incidence and mortality over time. In 2017, NCI and the American Society of Clinical Oncology's

CancerLinQ announced a partnership to enhance patient care and strengthen cancer surveillance through data sharing. Other examples of NCI resources that encourage data sharing include the Genomic Data Commons and The Cancer Imaging Archive.

## Strengthening Small Business Innovation and Commercialization

NCI provides support to US-owned small businesses aiming to develop and commercialize technologies that can be used to diagnose, treat, and prevent cancer. This support is provided through the congressionally mandated NCI Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs.

Successful commercialization of innovations developed with NCI SBIR funding means that doctors and their patients can access cutting-edge cancer-related technologies. In the past several years, such technologies have included the following:

- LumaGEM, a molecular breast imaging (MBI) technology, approved by the Food and Drug Administration (FDA) as an adjunct to mammography, to detect breast cancer in women with dense breasts. (Read more in *Detecting and Diagnosing Cancer* on page 26.)
- Percepta, the first genomics-based diagnostic test for lung cancer to receive Centers for Medicare and Medicaid Services coverage.
- SoftVue, a 3-dimensional ultrasound breast cancer imaging technology that uses sound waves to image the entire breast without compression and helps physicians distinguish normal tissues from areas of concern.
- Iobenguane I 131 (Azedra), the first FDA-approved intravenous cancer treatment that targets rare tumors in the adrenal gland. It is approved for adults and children age 12 or older whose tumors cannot be surgically removed, have spread beyond the original tumor site, or require systemic cancer therapy.
- De Las Mías, a mobile phone app developed for Spanish-speaking women that provides information on healthy living, with the goal of reducing cancer disparities.

NCI SBIR-funded technologies were used in more than 90 clinical trials in 2017 alone. Among these is an agent that received an orphan drug designation from FDA to treat glioblastoma multiforme, a cancer that has a 5-year survival rate of 15% or less among adults.

### Collaborations and Partnerships

NCI collaborates with institutes and centers across the National Institutes of Health, the US Department of Health and Human Services, and other federal agencies, nonprofit organizations, and companies to coordinate and leverage research activities, thereby accelerating cancer research advances and translating the findings to patients.

### Collaborating with Federal Agencies to Advance Cancer Research

NCI has collaborated extensively with multiple federal agencies to advance cancer research, including efforts to improve the drug development process and data sharing. The following examples are initiatives that demonstrate how different parts of the federal government can leverage each other's knowledge, resources, and infrastructure and operate more efficiently than if each organization worked in separate silos:

- NCI is partnering with the nation's two largest health systems, the US Department of Defense (DoD) and US Department of Veterans Affairs (VA), to incorporate proteogenomics (the activity and expression of the proteins that the genome encodes) into patient care through the Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) network.
- NCI and VA are also partnering to facilitate the enrollment of US veterans with cancer in NCI-sponsored clinical trials through the NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE) program.
- NCI and FDA are working together on a variety of activities, including implementation of the Research to Accelerate Cures and Equity (RACE) for Children Act, which requires that a novel drug developed for an adult cancer be considered for pediatric cancer when the

molecular target of the drug is relevant to a childhood cancer.

- NCI and the Centers for Disease Control and Prevention (CDC) collaborate with the American Cancer Society and the North American Association of Central Cancer Registries to produce the Annual Report to the Nation on the Status of Cancer, a yearly report describing recent cancer incidence and mortality trends.
- NCI also works with CDC on other cancer-related topics, including tobacco control, cancer vaccine programs, and cancer screening.

### Facilitating Access to Promising Agents

The NCI Formulary provides rapid access to therapeutic agents through partnerships with industry with the goal of accelerating cancer research by shortening the amount of time needed to start clinical trials that use drugs from more than one company. To date, the formulary contains 29 agents provided by 9 companies. Investigators at more than 300 sites can access these agents for research at no cost.

## Conducting Research at NCI

Investigators in the NCI intramural research program (IRP) conduct research across the cancer continuum. The IRP provides the flexibility to respond to unmet or emerging public health needs, provides a rich environment for collaboration, and is committed to training the next generation of researchers.

In addition, high-risk research and clinical trials that would be more difficult for the extramural community or industry to conduct are performed at NIH's Clinical Center, where compassionate patient care is combined with unparalleled opportunities for research. Examples of IRP activities are described throughout this plan and below.

### Pioneering Cancer Immunotherapies

NCI researchers have pioneered the development of cancer immunotherapies over the last 40 years. Research by IRP scientists was integral to the development of the CAR T-cell immunotherapies that were approved by FDA for certain types of leukemias and lymphomas in 2017. (Read more in *Treating Cancer* on page 32.) IRP scientists have also developed innovative methods to identify and test other types of adoptive cell transfer immunotherapies. This latter work has demonstrated promise in difficult-to-treat solid tumors, including in a patient with metastatic breast cancer and a patient with metastatic *KRAS*-driven colorectal cancer.

Intramural scientists and their collaborators have also identified ways in which tumors suppress the immune system's ability to fight them (read more in *Understanding the Mechanisms of Cancer* on page 10) and discovered genes that drive resistance to cancer immunotherapies.

### Developing Tools against Human Papillomavirus

Intramural NCI scientists have made critical discoveries about the biology of human papillomaviruses (HPV), leading to effective approaches that reduce the risk of several HPV-associated cancers. These approaches include HPV vaccines and HPV tests for use in cervical cancer screening. (Read more in *Preventing Cancer* on page 20.) Recently, IRP scientists demonstrated that a specific portion of the genome of HPV16, the most common type of HPV found in human cancers, is critical for the virus's ability to initiate tumor formation. The protein encoded by this genetic sequence may be a viable target for therapeutic intervention.

### Determining the Harms of Tobacco Use

NCI has a long history of studying the associations between tobacco use and cancer to inform public health decisions and interventions aimed at reducing the burden of tobacco-related disease. In addition to investigating the effects of cigarette smoking on cancer risk, IRP researchers are assessing the health risks of other tobacco and tobacco-related products, including smokeless tobacco, flavored cigarillos, electronic cigarettes, and hookahs (water pipes). Recently, IRP and FDA scientists showed that "low-intensity" smoking—fewer than 10 cigarettes per day—is associated with a significantly higher risk of death, including death from lung cancer, than never smoking. This study

provides further evidence that there is no safe level of tobacco smoking.

### Advancing Cancer Genomics

NCI's IRP has advanced our understanding of the genetic basis of cancer—from identifying genomic markers of cancer risk in population studies to characterizing the biological mechanisms of cancer at the genetic level in the laboratory.

For example, in a study of nearly 3,000 female survivors of childhood cancer who had been treated with radiation to the chest, IRP researchers identified a genomic marker associated with an increased risk of breast cancer later in life. In addition, IRP scientists have been leaders in studying the genetic basis of renal cell carcinoma (kidney cancer), elucidating the genetic subtypes of this cancer and translating that knowledge into new ways to treat patients.

NCI intramural scientists also led a recent study that identified four distinct genetic subtypes of diffuse large B-cell lymphoma, pointing the way toward future precision medicine strategies.

Another group of IRP investigators recently found that the *Klf4* gene is involved in promoting the metastasis (spread) of melanoma, breast cancer, and pediatric rhabdomyosarcoma tumors. Understanding the metastatic process is necessary to develop approaches to limit the spread of cancer.

### Addressing the Challenge of Rare Tumors

NCI's IRP is committed to making progress against rare cancers and diseases. Leveraging the unique resources of the NIH Clinical Center, IRP investigators bring patients with these diseases from around the world to Bethesda, MD, to participate in clinical trials.

For example, IRP investigators are leading the development of a targeted therapy for children with neurofibroma tumors. Recently, IRP researchers demonstrated the feasibility of using whole-body MRI as a comprehensive cancer screening method for patients with Li-Fraumeni syndrome (LFS), a rare inherited disorder that leads to a higher risk of certain cancers. Individuals with LFS have an approximately 50% chance of developing cancer by age 40 and up to a 90% chance by age 60. Many patients with LFS develop more than one primary cancer during their lifetimes.

To make additional progress, NCI launched the Rare Tumors Initiative in 2013 and the Rare Tumor Patient Engagement Network in 2018 as part of the Cancer Moonshot.

## Frederick National Laboratory for Cancer Research

The Frederick National Laboratory for Cancer Research (FNLCR) is the only national laboratory in the United States dedicated exclusively to biomedical research. As a government-owned, contractor-operated facility, it offers unique partnership opportunities for academia, government, and the private sector to address the most difficult challenges in cancer prevention, treatment, and control. Among its many initiatives, FNLCR is integral to the cancer research activities described below.

### Finding Better Treatments for RAS-Driven Cancers

More than 30% of all human cancers—including 95% of pancreatic cancers and 45% of colorectal cancers—are driven by mutations in *RAS* genes. Yet, we do not have effective approaches for targeting mutant RAS. For this reason, understanding the biology of RAS proteins is critical to finding better treatments for patients with many different types of cancers. Through the NCI RAS Initiative, FNLCR has distributed RAS research reagents to more than 150 laboratories worldwide and has helped identify new compounds that might be used against RAS-driven cancers.

### Using High-Resolution Imaging to Acquire the Best Quality Data

Through the National Cryo-Electron Microscopy (cryo-EM) Facility, operated by FNLCR, NCI assists cancer researchers who are engaged in structural biology studies but lack access to the latest technologies at their own institutions to capture exceptional imaging at resolutions near the atomic level. The facility has completed more than 70 projects for research laboratories across the country since it opened in 2017.

# Professional Judgment Budget Proposal for Fiscal Year 2020

(Dollars in millions)

| | | |
|---|---|---|
| **FISCAL YEAR 2018 NCI BASE APPROPRIATION** | **$5,665** | |
| **TOTAL BUDGET INCREASE**<br>Proposed Allocation | **$662†** | **$322** Inflation Adjustment*<br>**$70** Understanding the Mechanisms of Cancer<br>**$70** Preventing Cancer<br>**$30** Detecting & Diagnosing Cancer<br>**$85** Treating Cancer<br>**$50** Advancing Public Health in Cancer<br>**$35** Strengthening the Cancer Research Enterprise |
| **FY 2020 BASE BUDGET PROPOSAL** | **$6,327** | |
| **FY 2020 CANCER MOONSHOSM FUNDING** | **$195** | |
| **FY 2020 TOTAL** | **$6,522** | |

* Adjustment includes inflation for the 2 years between FY 2018 and FY 2020
† In addition to the inflation adjustment, the increase of $662 million includes $340 million for additional cancer research in six areas

This *Fiscal Year 2020 Professional Judgment Budget Proposal* includes investments in six areas needed to advance cancer research. Included in this investment is a significant increase to the Research Project Grants (RPG) pool, one of the best ways to support investigator-initiated science. Early-stage investigators will continue to be a high priority within the RPG pool.

NCI will also increase funding to support clinical trials through meaningful investments in the National Clinical Trials Network and the NCI Community Oncology Research Program. NCI will support additional funding for training grants and professional development opportunities to support the next generation of diverse researchers throughout their careers. Other increases include those for the Specialized Programs of Research Excellence and the NCI Cancer Research Data Ecosystem.

This budget proposal also includes Cancer Moonshot funding authorized in the 21st Century Cures Act. As funding for the Cancer Moonshot peaks in FY 2019 and declines by more than half in FY 2020, an increase to the overall budget will ensure that research keeps pace with the progress made so far through the Cancer Moonshot. This budget proposal lays the foundation for promising advances in cancer research. However, further investments will need to be made to ensure this progress is sustained.

## The Cancer Moonshot

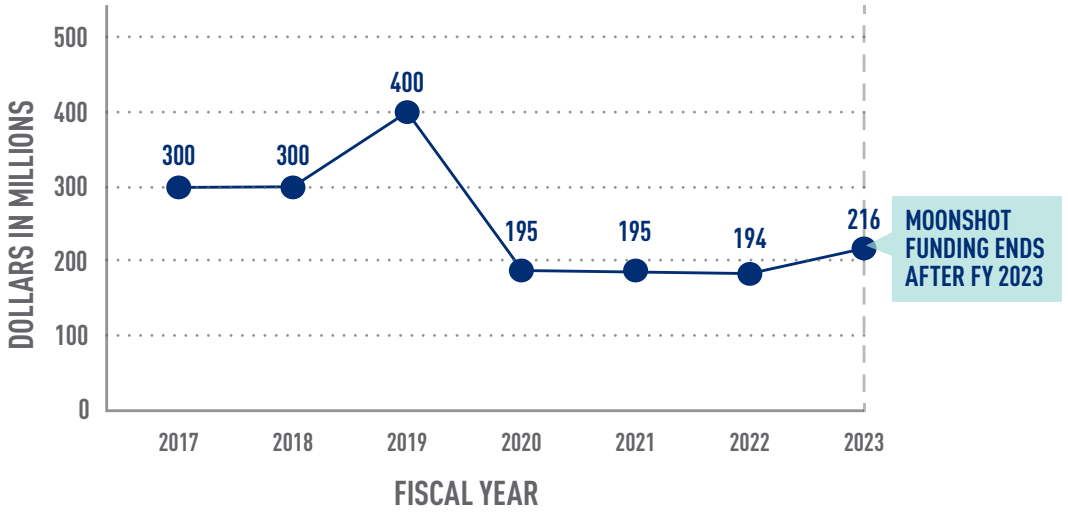
The Cancer Moonshot℠, announced in December 2016, is a national effort to accelerate the pace of cancer research by breaking down barriers to progress by enhancing data sharing and facilitating collaborations. A Blue Ribbon Panel (BRP) convened by NCI as a working group of the National Cancer Advisory Board recommended 10 of the most compelling research opportunities that were poised for acceleration.

The passage of the 21st Century Cures Act that same year authorized a total of $1.8 billion to fund the Cancer Moonshot over 7 years, from FY 2017 through FY 2023, at varying annual amounts. Since then, teams consisting of more than 250 scientific experts and staff from NCI and across the National Institutes of Health have been formed to implement the BRP recommendations.

The $300 million made available for FY 2017 enabled NCI to support research that aligned with the BRP recommendations. In FY 2018, NCI began funding new research networks to advance adult and pediatric immuno-oncology, generate human tumors atlases, increase screening for inherited cancers, and other initiatives.

In just the first 2 years, the Cancer Moonshot has provided the research community with important new opportunities to pursue critical cancer research. NCI is currently planning activities for FY 2019 through the last year of authorization, FY 2023.

### Cancer Moonshot Funding Authorized Under the 21st Century Cures Act





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