



NATIONAL CANCER INSTITUTE

Annual Plan & Budget Proposal for Fiscal Year 2017

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A Transformational Moment in Cancer Research



When I speak with leading cancer researchers in the United States and around the world, I hear unprecedented optimism that we are on the verge of pivotal advances in oncology. This sentiment is based on progress in many important areas, including immune-based therapies, genomics, advanced imaging technologies, new laboratory models of human cancer, precision medicine, and more.

Key aspects of our understanding of and approach to cancer have been transformed based on years of investment in biomedical research. We are increasingly able to treat cancer with greater precision by identifying the molecular abnormalities that drive each person's cancer and targeting therapies to each patient, ultimately improving outcomes and providing hope.

This promise of precision medicine has already been realized for treating some cancers, and we foresee greater progress in preventing, screening, and treating other cancers and even other diseases. Cancer research, therefore, offers a model for other fields of biomedical research that seek to leverage genetic and other molecular information to administer precise and effective interventions to treat disease.

At NCI, we are advancing precision oncology while managing our resources to take full advantage of the most promising scientific opportunities. It is essential that NCI support the full continuum of scientific research—from basic biological research, to population-based studies, to cutting-edge clinical trials—as virtually all advances in cancer depend on many fields of science.

With steady and sustained budget increases and a cadre of talented researchers, a new era of cancer medicine is well within reach.

Although dramatic progress is being made, important scientific opportunities lie before us. With steady and sustained budget increases and a cadre of talented researchers, a new era of cancer medicine is well within reach.

Despite careful management of the NCI budget, many meritorious research

proposals—including some bold concepts—must go unfunded each year due to the fiscal constraints we have been operating under for more than a decade. There is little doubt that budget constraints have resulted in missed scientific opportunities.

With the exception of the one-time increase allocated in the American Recovery and Reinvestment Act, federal investment in cancer research has been stagnant since 2003. During this same period, the costs of conducting research have escalated as inflation has substantially eroded NCI's purchasing power. As a result, competition for NCI grants has been fierce, and some young researchers, frustrated by a lack of funding, have abandoned careers in medical research.

The current budget situation has hindered NCI's ability to optimally fulfill its mission and promise to the American public: to foster rapid progress and reduce the burden of cancer.

Working closely with its advisory boards, NCI senior leadership has made difficult funding choices, reducing funding for some worthwhile programs and initiatives and curtailing funding altogether in some cases.

In the budget table that follows, NCI recommends a funding increase of 7 percent over the fiscal year 2016 level to pursue promising research opportunities that improve our understanding of cancer and reduce the burden of the disease. These research opportunities are among those for which additional funding would greatly speed the progress against cancer.

But a 7 percent increase can only be viewed as an initial down payment. Steady funding increases, sustained over time, are necessary to restore NCI's purchasing power and accelerate scientific discovery in ways that significantly reduce the burden for people with all types of cancer.

An annual increase of 7 percent for the next 10 years is necessary to achieve these goals. These steady increases will result in a fiscal year 2026 budget for NCI that is twice what it is today.

NCI recommends a funding increase of 7 percent over the fiscal year 2016 level to pursue promising research opportunities that improve our understanding of cancer and reduce the burden of the disease.

As NCI's leader, I am continually inspired by the incredible dedication and passion of the institute's staff and researchers, as well as the dedication and passion of cancer researchers across the country and around the world. We understand that patients and their loved ones expect and deserve continued progress and that we have an obligation to meet their expectations.

Douglas Lowy, M.D.
Acting Director, National Cancer Institute

NCI recommends a funding increase of 7 percent over the fiscal year 2016 level to pursue promising research opportunities that improve our understanding of cancer and reduce the burden of the disease.

NATIONAL CANCER INSTITUTE BUDGET PROPOSAL & PRIORITIES FISCAL YEAR 2017

(Dollars in millions)

FISCAL YEAR
2016 ESTIMATE

\$5,098

REQUESTED ADDITIONAL RESOURCES

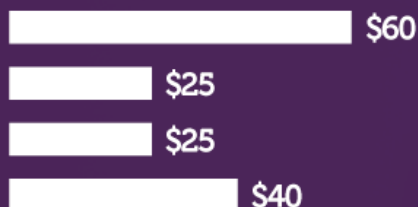
Examples of areas where improved funding would greatly speed progress



UNDERSTANDING CANCER

\$150

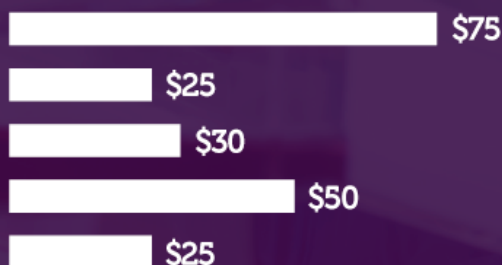
- Cancer Causes & Disease Progression
- Biology of Cancer Health Disparities
- Biology of the Immune System
- Genomic Analysis of Tumors



BRINGING CANCER RESEARCH TO THE PUBLIC

\$205

- Precision Medicine Clinical Trials*
- Additional Treatment Trials
- Translational Research†
- Prevention & Early Detection
- Bioinformatics‡



**TOTAL ADDITIONAL
RESOURCES**

\$355

**TOTAL NCI FY 2017
BUDGET
RECOMMENDATION**

\$5,453

*Including pediatric precision medicine clinical trials

†Transferring basic scientific knowledge into new treatments

‡Using computers to store, manage, and analyze large sets of biological data



Progress & Trends:
Decreased Mortality,
Increased Survival
Rates

Decreasing cancer death rates and increasing numbers of cancer survivors are important indicators of the progress we are making in diagnosing and treating cancer, but much work remains. Too many people still face a diagnosis of cancer, and far too many still die from the disease.

U.S. Trends

Before 1990, overall age-adjusted cancer mortality rates increased for several decades. Since the mid-1990s, however, they have dropped steadily. Mortality rates are decreasing for most cancers, including those that arise at the four most common sites: the lung, breast, colon/rectum, and prostate.

These improvements in mortality rates have been accompanied by a substantial increase in the number of cancer survivors. Whereas cancer survivors accounted for about 2.5 percent of the U.S. population in 1992, it is estimated that they will account for about 5.4 percent of the population in 2024.

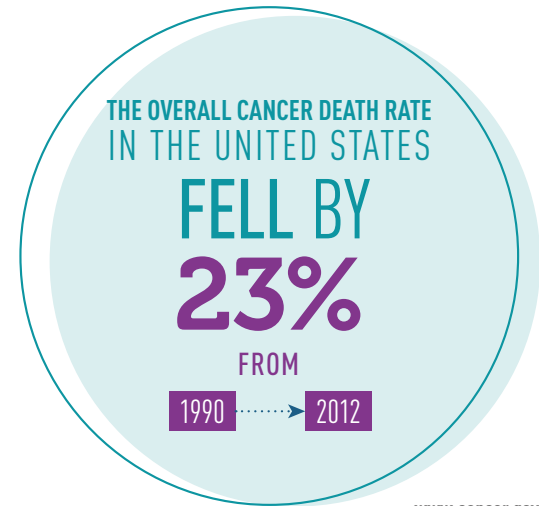
For many of these survivors, long-term effects, both physical and psychological, may remain. Recognizing this, survivorship research remains a key component in NCI's research portfolio.

Despite these advances, it is estimated that approximately 590,000 adults and nearly 2,000 children and adolescents will die from cancer in the United States in 2015 and that 1.66 million new adult cancer cases and 15,000 new childhood and adolescent cancer cases will be diagnosed.

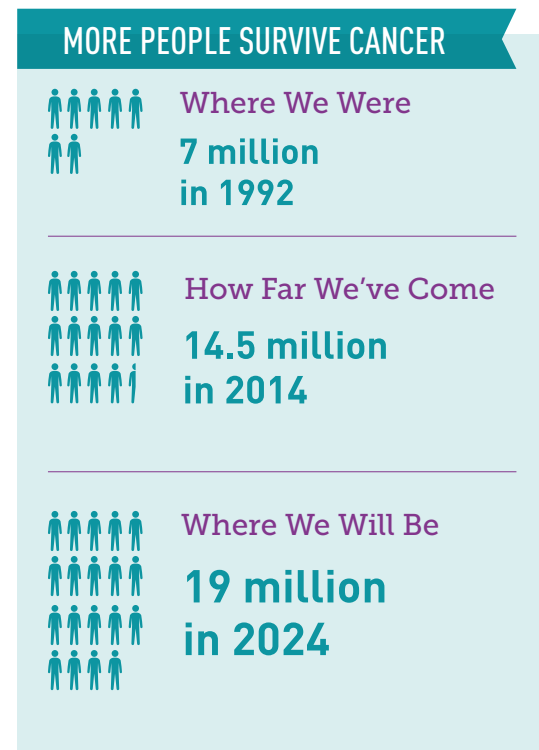
In addition, our progress in preventing, diagnosing, and treating cancers is not universal for all forms of the disease. The mortality rates for some cancers have actually increased.

Because older age is a major risk factor for developing cancer, improved life expectancy by itself will lead to a rise in the total number of cancer cases in the United States. Therefore, although the age-adjusted rates at which cancer develops are expected to continue to decline, the aging of the U.S. population means that the total number of cancers will increase.

These projected increases imply that intensive and sustained research efforts against cancer will continue to be critical. NCI continues to employ every aspect of its portfolio to better prevent, diagnose, and treat cancer, but these efforts must be enhanced to keep up with the changing demographics of our society.



www.cancer.gov
Source: SEER Cancer Statistics Review 1975-2012

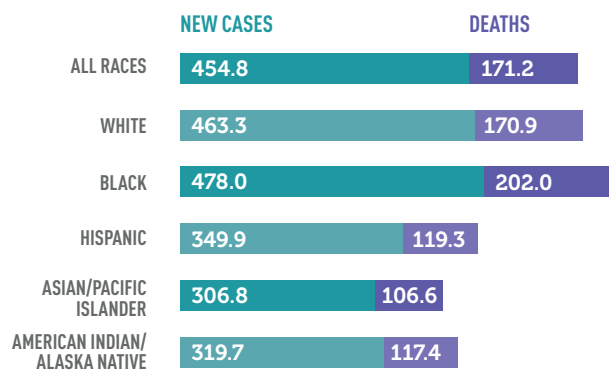


www.cancer.gov
Source: American Cancer Society, Cancer Treatment & Survivorship Facts & Figures 2014-2015

Racial/Ethnic Disparities

Although declines in overall cancer incidence and mortality have been observed for most racial and ethnic groups in the United States, certain groups continue to have higher incidence and mortality rates for some cancers than the general population.

NUMBER OF NEW CASES & DEATHS PER 100,000 PERSONS BY RACE/ETHNICITY: ALL CANCER SITES



www.cancer.gov
Source: SEER 18, 2008-2012

For example, in 2012, the rates of colorectal cancer incidence and mortality among African Americans were 22 percent and 36 percent higher, respectively, than the rates observed for the general population. For multiple myeloma, the incidence and mortality rates in 2012 were 116 percent and 85 percent higher, respectively, for African Americans than for the general population.

Among gender-specific cancers, the rates of prostate cancer incidence and mortality among African American men from 2008 through 2012 were 56 percent and 116 percent higher, respectively, than the rates for men in the general population. During the same period, the rates for cervical cancer incidence were 29 percent and 19 percent higher among Hispanic and African American women, respectively, than among women in the general population, and the corresponding rates of cervical cancer mortality were 17 percent and 74 percent higher for Hispanic and African American women, respectively.

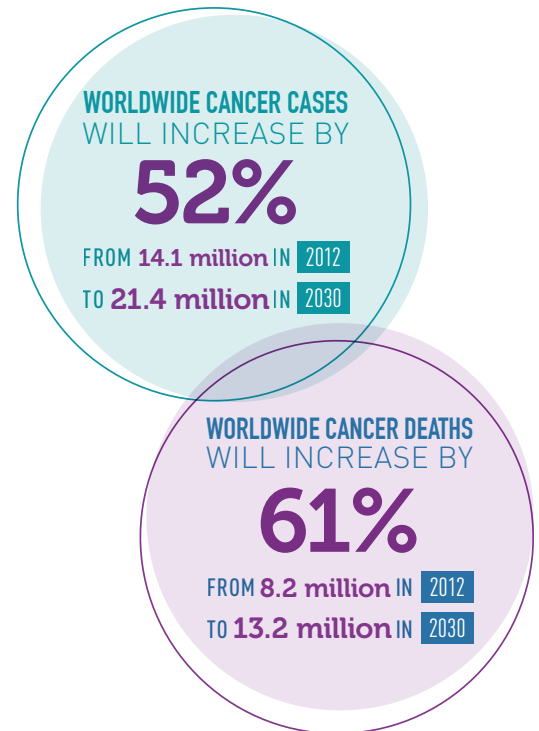
Global Trends

Improvements in nutrition, health care, and other factors are increasing life expectancy for most of the world. However, this benefit is accompanied by an increase in many diseases associated with an aging population, including cancer, and this trend is being exacerbated by greater tobacco consumption in many low- and middle-income countries.

The projected increases in cancer rates in the U.S. and worldwide imply that intensive and sustained research efforts against cancer will continue to be critical. NCI continues to employ every aspect of its portfolio to better prevent, diagnose, and treat cancer, but these efforts must be enhanced to keep up with changing U.S. and global demographics.

Obesity

Over the past few decades, the incidence of obesity has risen markedly in the United States and in many other countries around the world. Although the so-called obesity epidemic has been most commonly linked to the rising incidence of diabetes and related conditions, it also has substantial implications for cancer research and cancer control, since obesity is associated with increased risks of developing cancer at many sites.



www.cancer.gov
Source: American Cancer Society: Global Cancer Facts & Figures, Second Edition

The National Cancer Program: Driving Discovery

NATIONAL
CANCER
INSTITUTE

NCI coordinates the National Cancer Program and supports it by providing funding and resources to individual researchers and institutions, providing leadership to national infrastructures that care for patients and develop new methods to treat and prevent cancer, and conducting research in especially challenging areas.

Progress against cancer depends on many types of research—including basic, translational, and clinical—across different research areas, from the biology of cancer cells to studies of large populations.

Regardless of the research type or area, supporting the best science and the best scientists is of paramount importance to NCI.

New Approaches to Funding Researchers

NCI continues to develop new funding opportunities that adapt to changes in the way that science is conducted.

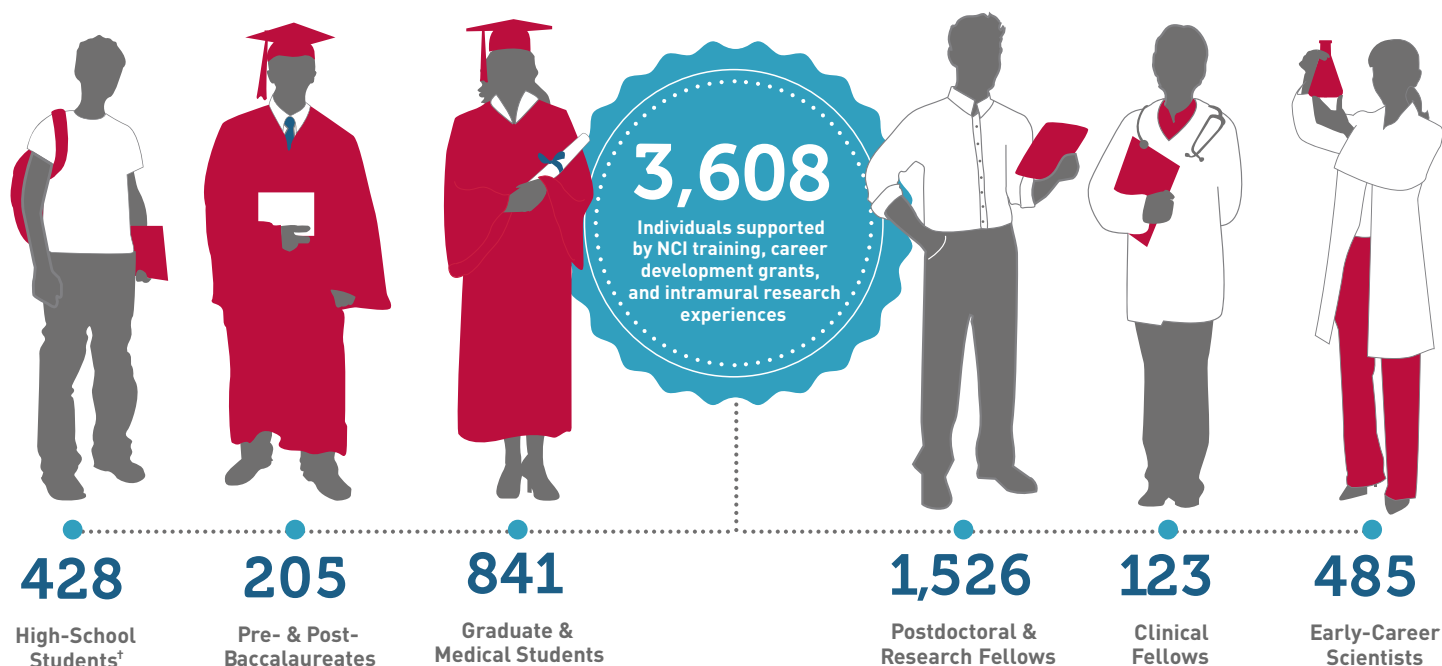
Support for the best science underpins everything NCI does; therefore, recruiting outstanding young investigators with great potential is a priority for the institute. However, the uncertainty of a successful career due to a lack of funding opportunities has made attracting and retaining the best minds to the field of cancer research today a challenge.

NCI is also committed to supporting the training and development of a strong workforce of cancer researchers that spans the career continuum. Due to current limitations in funding, however, the early careers of graduate students, postdoctoral fellows, and young investigators may be hampered by low salaries, many years spent in training positions, and still more years in an independent research position before they obtain an NIH grant for their research.



NATIONAL CANCER INSTITUTE Training The Workforce

In FY 2014, NCI supported 3,608 emerging cancer researchers through training and career development grants and intramural research experiences.*



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

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

www.cancer.gov

Source: <http://www.cancer.gov/cct> | <http://crchd.cancer.gov>

For most of the past 50 years, at least 30 percent of grant applications were funded, dipping to 25 percent during periods of lean budgets. Today, the percentage of successful applications hovers in the mid-teens, far lower than at any other time.

Although NCI is actively building a cancer research workforce for the future, these efforts will appear hollow without strong support for funding these young scientists. Even established researchers are now forced to devote too much time to securing funding rather than conducting research or training the next generation of scientists.

Moreover, when funds are limited, there is a tendency to support less risky research. However, high-risk research, the fruits of which may take several years to realize, is often where the biggest breakthroughs are made. Therefore, NCI has taken steps to provide incentives to researchers who propose and conduct high-risk research.

In 2014, NCI established the Outstanding Investigator Award, and the first awardees will be announced in the fall of 2015. This new R35 funding mechanism is designed to provide longer-term support—7 years—and more than twice the dollar amount of an average R01 investigator-initiated grant. These awards are given to experienced investigators who are likely to continue conducting seminal cancer research and mentoring the next generation of cancer researchers. With this support, investigators may pursue research that might be viewed as too high-risk to be funded through regular grant mechanisms.

In addition, through mechanisms such as R21 exploratory grants, NCI seeks to help investigators conduct other potentially new and exciting but high-risk studies.

The Provocative Questions initiative is another approach developed by NCI to stimulate the research community and provide a new form of funding. Through this initiative, NCI is supporting research, including basic and applied, in a number of important areas that have been understudied, neglected, paradoxical, or difficult to address in the past.

THE PROVOCATIVE QUESTIONS INITIATIVE

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

THE INITIATIVE HAS FUNDED

188

GRANTS

WITH MORE THAN

\$70

MILLION

www.cancer.gov

Source: NCI Center for Strategic Scientific Initiatives

University of Kentucky Markey Cancer Center



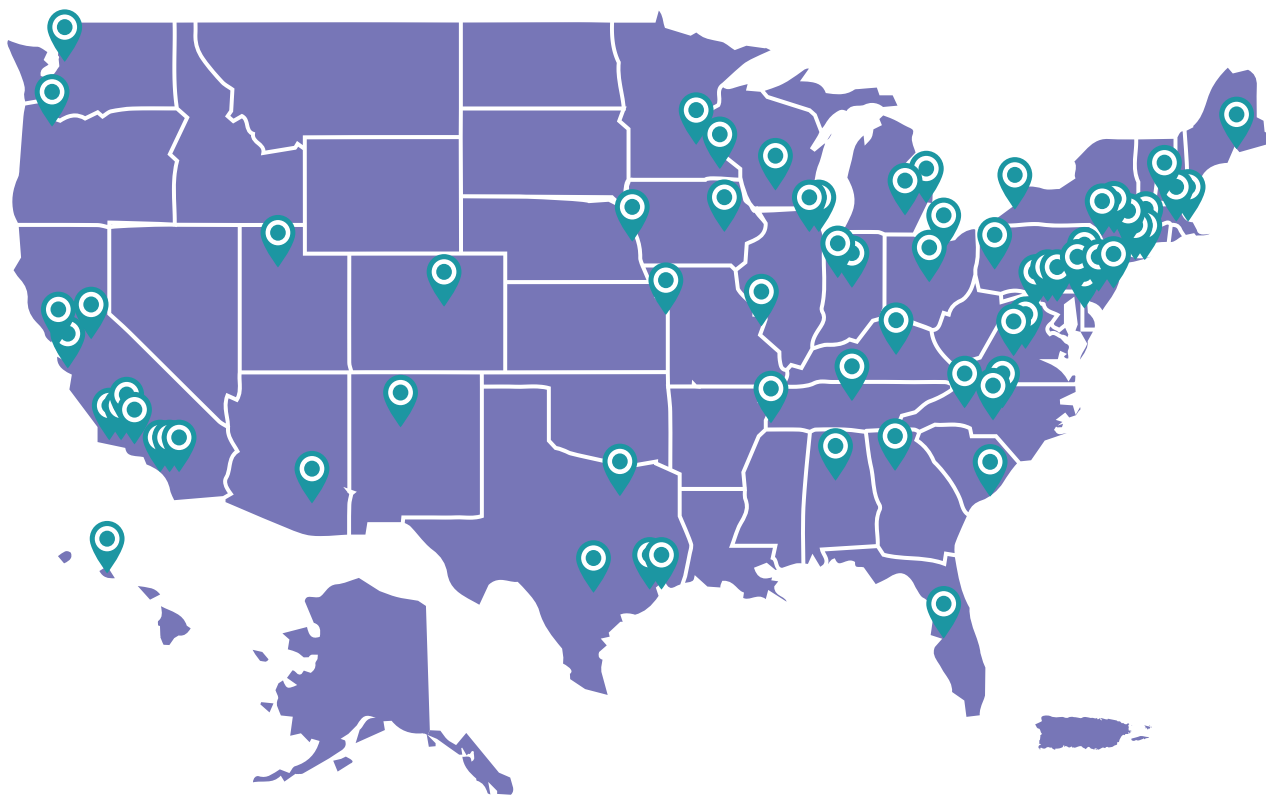
NCI-Designated Cancer Centers

The NCI-Designated Cancer Centers program is a major anchor of the nation's cancer research effort.

At any given time, hundreds of cutting-edge research studies are under way at NCI-Designated Cancer Centers, ranging from basic laboratory research to clinical assessments of new treatments.

Each NCI-Designated Cancer Center receives a core support grant from NCI that funds the critical research infrastructure of the center, in addition to the funding received from individual competitive research grants and contracts with NCI.

The funding provided by the core grants is essential for the efficient conduct of research at the centers and for driving the nation's progress against cancer.



www.cancer.gov

The 69 NCI-Designated Cancer Centers are at the forefront of NCI-supported efforts at universities and cancer research centers across the United States. The centers are developing and translating scientific knowledge from promising laboratory discoveries into new treatments for cancer patients. There are 17 cancer centers, 45 comprehensive cancer centers, and 7 research centers.

NCI's National Clinical Trials Enterprise

NCI has a long history of supporting both small early-phase trials as well as large-scale trials, many of which have led to changes in standard medical practice. People with cancer now live longer lives in part because of strategies that have come from NCI's clinical trials program.

To respond rapidly to new scientific opportunities, especially in conducting the new generation of precision medicine clinical trials, NCI created the National Clinical Trials Network (NCTN).

Precision medicine trials require sophisticated and expensive technologies and clinical processes that have not typically been a part of most clinical trials.

In addition to the higher cost of conducting precision medicine clinical trials, NCI is now providing a higher percentage of cost reimbursement to the physicians who are treating participants enrolled in trials.

Although the NCTN is designed to carry out all aspects of precision medicine trials, NCI is unable to fully support it and must rely on the institutions and others involved in the network to cover some costs.

IN 2015 NCI'S NATIONAL CLINICAL TRIALS NETWORK INCLUDED:

3,100
INSTITUTIONS

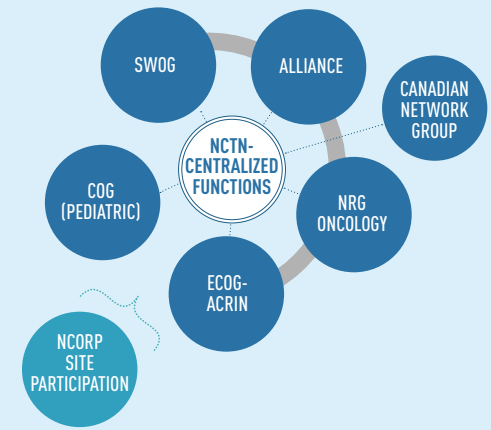


www.cancer.gov

Source: NCI Cancer Therapy Evaluation Program

NATIONAL CANCER INSTITUTE National Clinical Trials Network

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



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

www.cancer.gov
www.cancer.gov/clinicaltrials/nctn

Although these partnerships are highly effective and appropriate for some trials, there are some clinical questions for which there are no obvious partners. It is NCI's responsibility to pursue these trials, especially in the case of rare cancers, but, as in other areas of NCI-supported research, current funding levels constrain maximizing their pursuit.

In addition, in 2014, the institute launched the NCI Community Oncology Research Program (NCORP), a community-based initiative that brings clinical trials, as well as research aimed at improving the efficiency and quality of delivered health care, to people in their own communities. NCORP provides an important connection to community-based cancer care, ensuring that people have access to the benefits of the latest research regardless of where they live.

Overcoming Cancer Health Disparities

NCI's Center to Reduce Cancer Health Disparities (CRCHD) is a major component of the institute's efforts to address the unequal burdens of cancer experienced by certain racial and ethnic groups in our society. Finding ways to reduce these cancer health disparities is also a major focus of NCORP.

NCI supports a wide range of research, including basic biological research, to increase our understanding of the causes of cancer health disparities and to develop ways to mitigate their effects and, ultimately, eliminate them.

NCI also supports studies of health care access and utilization, their effects on health-related outcomes, and epidemiologic studies examining the role of obesity and other risk factors in cancer health disparities.

NCI is also committed to training underrepresented minorities in cancer research in general and cancer health disparities in particular. These training programs include the Continuing Umbrella of Research Experiences (CURE) and Partnerships to Advance Cancer Health Equity (PACHE).



The NCI Community Oncology Research Program provides care in community-based health care practices across the United States.

NCI CRCHD's Continuing Umbrella of Research Experiences (CURE) program provides

BIOMEDICAL RESEARCH TRAINING AND CAREER DEVELOPMENT FUNDING OPPORTUNITIES

to more than **3,000** underrepresented scholars from high school through investigator level

www.cancer.gov

Addressing the Unique Challenges of Childhood Cancer Research

NCI recognizes the importance of research that focuses on cancers in children and adolescents and has an extensive biomedical research portfolio that relates, directly or indirectly, to childhood cancer. This portfolio includes basic scientific research, which enhances our understanding of the fundamental mechanisms of cancer, and clinical research, which evaluates new therapies and other interventions for safety and effectiveness.

NCI's Intramural Research Program

Some of NCI's budget supports the intramural research program and the research of scientists who work at the NIH Clinical Center and in offices and laboratories located in Bethesda, Rockville, and Frederick, Maryland. These intramural investigators conduct basic, clinical, and population-based research, including the study of rare cancers, and are encouraged to explore the translation of relevant findings from the laboratory to the clinic.

Intramural researchers at this center are able to quickly test new approaches to cancer prevention and treatment. The ability of the NIH Clinical Center to treat patients from all over the world facilitates clinical research on rare cancers, which may help patients with these diseases and produce insights relevant to more common cancers.

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

With both academic and private sector partners, intramural researchers can undertake longer term projects that may be difficult, if not impossible, through traditional funding mechanisms.

Bioinformatics to Accelerate Research

Bioinformatics, which enables the management and use of very large sets of complex molecular and clinical data, has become a core component of NCI's research enterprise.

The data center at NCI's Frederick National Laboratory for Cancer Research in Frederick, Maryland, provides high-performance, high-capacity computing support for these efforts.

The Cancer Genome Atlas, a joint effort by NCI and the National



Annette Abrams, a patient of Daniel H. Fowler, M.D., of NCI's Experimental Transplantation and Immunology Branch, stands by a mosaic she created while undergoing treatment. The art is on display at the NIH Clinical Center.

Credit: National Cancer Institute (Rhoda Baer)

Human Genome Research Institute to survey the landscape of genomic alterations in more than 30 different types of cancer, has generated 2.5 petabytes (2.5 million gigabytes) of next-generation sequencing data from several different technology platforms.

NCI is establishing the Genomic Data Commons (GDC) to store, analyze, and distribute cancer genomics data generated by NCI and other research organizations. Currently, these data and associated information are being stored in many different repositories, which is inefficient, confusing, and a barrier to research. The GDC, a centralized repository, will address these problems by putting the data in one place that will be widely accessible.

An additional impetus for the GDC is to reduce the total cost of ownership of genomic data for NCI. Having many smaller repositories makes it harder for researchers to find and retrieve the data they are looking for. It also creates many systems, all at least slightly different, that need to be maintained and upgraded as the state of science changes. This is costly and hard to manage, coordinate, and sustain.

Strong, continuous funding for bioinformatics is needed to:

- increase the capacity of the GDC and enable it to handle additional data types generated by precision medicine research
- explore the development of clinical bioinformatics, in which biological information is integrated with medical information to enhance precision health care
- support the use of new experimental models of human cancer in cancer drug discovery and development and in studies of cancer cell biology

Frederick National Laboratory for Cancer Research

What is today the Frederick National Laboratory for Cancer Research (FNLCR) had its beginning in a 1971 designation by President Nixon. In 1975, it became the only Federally Funded Research and Development Center (FFRDC) dedicated to biomedical research.

Overseen by NCI, this FFRDC provides rapid response capabilities and one-of-a-kind resources for the entire biomedical research community using a unique contract mechanism that brings public and private partners together to solve difficult medical research challenges.

The FNLCR provides scientific tools, services, and information to support



Dan Oleyar collects data center metrics at the Advanced Technology Research Facility at the Frederick National Laboratory for Cancer Research in Frederick, Maryland.

Credit: National Cancer Institute

researchers and to enable and expedite their investigations. Examples include support for drug discovery and development and for the characterization and quality-control assessments of nanoparticles being developed for cancer diagnosis and treatment.

As a national resource, the FNLCR provides cancer researchers a bridge between basic research and clinical practice with support that is not readily available elsewhere.



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

Credit: National Cancer Institute



Opportunities in Precision Oncology

In the very near future, a patient's cancer will be extensively characterized for mutations and other molecular abnormalities, and his or her treatment will be based on the identified molecular changes instead of where the cancer originated in the body. This approach is part of what is called precision (or personalized) medicine.

The greater molecular and mechanistic understanding of cancer that we are gaining—and applying toward the development of new therapies—is also directly applicable to cancer prevention and screening.

To speed progress in this area, President Obama announced the Precision Medicine Initiative (PMI) on January 30, 2015. The PMI is a \$215 million proposed investment to accelerate biomedical research and provide clinicians with new therapies and tools to select the treatments and interventions that will be most effective for individual patients.

Advancing Precision Medicine in Oncology

The PMI includes \$70 million in increased funding for NCI to advance the field of precision medicine in oncology. Oncology is an appropriate choice to begin this ambitious initiative, since precision medicine focuses mainly on genes, and cancer is a disease of the genome.

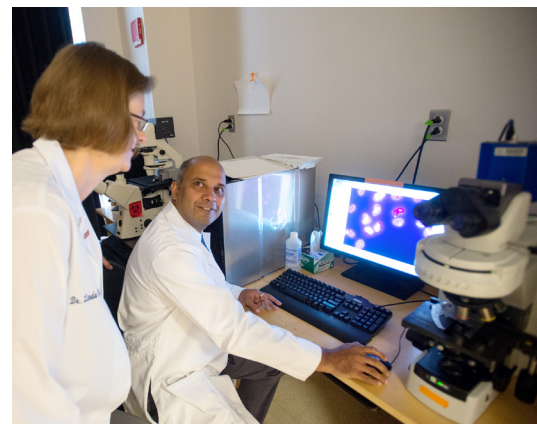
At the time of the PMI's announcement, NCI was well along the path toward precision medicine, but steady and sustained funding is needed to capitalize on the exciting opportunities now at hand.

Expanding Precision Medicine Trials

NCI's efforts in precision medicine include the development of clinical trials for patients whose cancers will be profiled and whose treatments will be based on the molecular abnormalities in their tumors. These trials include Lung-MAP, ALCHEMIST, and NCI-MATCH.

More robust funding would allow NCI to:

- expand NCI-MATCH to include additional targeted drugs and increase the number of genetic alterations being investigated
- accelerate the launch of Pediatric MATCH
- collect and analyze genomic data sets to increase our understanding of the genetic alterations associated with cancer



Shridar Ganesan, M.D., Ph.D. (right), of Rutgers Cancer Institute of New Jersey, studies genomic changes in cancers that can be therapeutically targeted.

Credit: National Cancer Institute

NATIONAL CANCER INSTITUTE

ADVANCING PRECISION ONCOLOGY

UNDER THE NATIONAL PRECISION MEDICINE INITIATIVE

Precision oncology: using molecular information about a patient's cancer to inform treatment

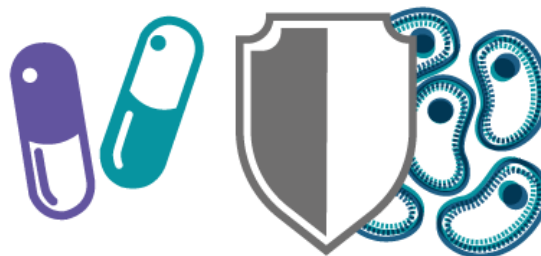
To make precision oncology a reality in everyday clinical practice, NCI is leading research to:

EXPAND PRECISION MEDICINE CLINICAL STUDIES TO ADULTS AND CHILDREN IN THEIR COMMUNITIES



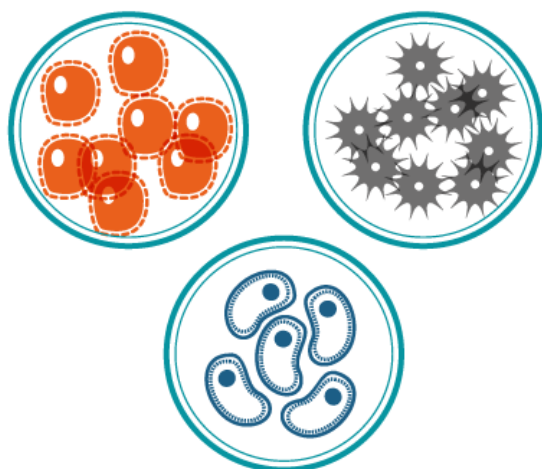
to test new cancer treatments

OVERCOME DRUG RESISTANCE



to learn why cancer treatments stop working in many patients

INCREASE THE NUMBER OF LABORATORY MODELS OF HUMAN CANCER



to test potential treatments and learn more about cell changes that drive cancer

BUILD A KNOWLEDGE NETWORK THAT INTEGRATES CANCER GENOMIC INFORMATION WITH CLINICAL INFORMATION



to serve as a resource for scientists, health care professionals, and patients

- establish a national knowledge network to house and integrate genomic information from tumors—annotated with clinical information, including treatment response and patient outcomes information—as a resource for scientists, health care workers, and patients

Enhancing Drug Discovery and Development

Another goal of precision medicine is the development of new treatments that are more effective and less toxic than traditional treatments to improve the care of patients with cancer.

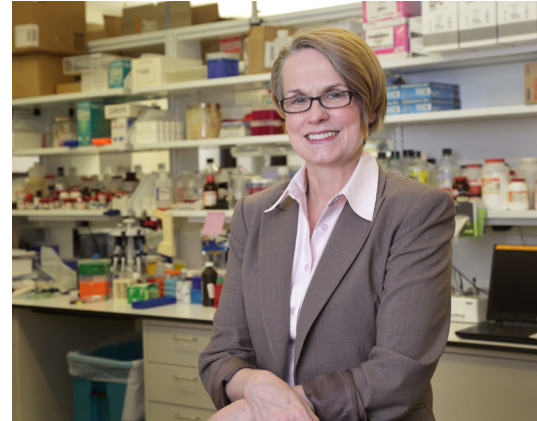
Historically, NCI has played a vital role in cancer drug discovery and development, and, today, that role continues. Frequently, NCI's drug development efforts focus on unmet needs that are not being adequately addressed by the private sector. The success of NCI's efforts is reflected in the fact that the institute has been involved in the discovery or development of a large percentage of the anticancer therapeutics on the market today.

To speed the delivery of these therapies to patients with cancer, NCI's Experimental Therapeutics Program (NExT) supports the most promising new drug and biologic agent discovery and development projects through collaborations with partners in academia, government, and industry.

The PMI would provide clinicians with new therapies and information to select treatments that will work best for each patient.

Under the initiative, NCI would:

- greatly expand the number of human cancer models to facilitate the study of human cancer biology, drug discovery and development, and therapy selection
- test new therapies against some childhood cancers and common cancers in adults
- investigate and develop approaches for overcoming the difficult problem of acquired resistance to cancer treatments



While in NCI's Center for Cancer Research, Susan Bates, M.D., studied a compound that would become the cancer drug romidepsin (Istodax®).

Credit: National Cancer Institute (Bill Branson)

Developing New Human Cancer Models

To support NCI's anticancer drug discovery program, the institute established the NCI-60 Human Tumor Cell Line Screen in 1990. Tens of thousands of compounds have been tested using this screen, generating the largest cancer pharmacology database in the world.

As valuable a resource as the NCI-60 cell line screen has been, it does have limitations. Aside from including only a few cell lines for just a few cancer types, we don't know how representative the cell lines are with respect to their corresponding cancer types.

New human cancer models and refinements in the methods used to generate them are making human cancer models resemble human disease more closely. Furthermore, technological advances are making it easier to study the biological effects of specific gene mutations and potential therapies in these models.

These advances have considerable potential to provide additional insight into:

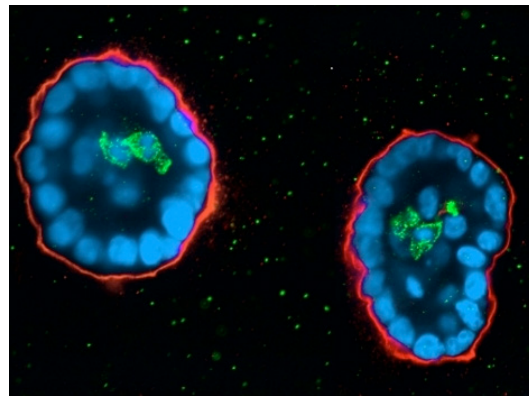
- the development of cancer
- the role of the tumor microenvironment
- responses to new therapeutic interventions
- treatment selection
- understanding and overcoming drug resistance

These new human cancer models should enhance our drug discovery and development efforts and increase our understanding of human cancer cell biology.

With adequate funding, the institute would be able to molecularly characterize the tumors of every patient treated in an NCI-sponsored clinical trial and generate models from those tumors, greatly accelerating the evolution of precision medicine and its implementation into routine cancer care.

Harnessing the Promise of Immunotherapy

Research in cancer immunotherapy has led to the development of several new methods of treating cancer by restoring or enhancing the immune system's ability to fight the disease.



Cancer cell spheres, or spheroids, formed during three-dimensional culture of cells from a breast cancer cell line. Spheroids can be used to screen drugs or study cancer cell biology.

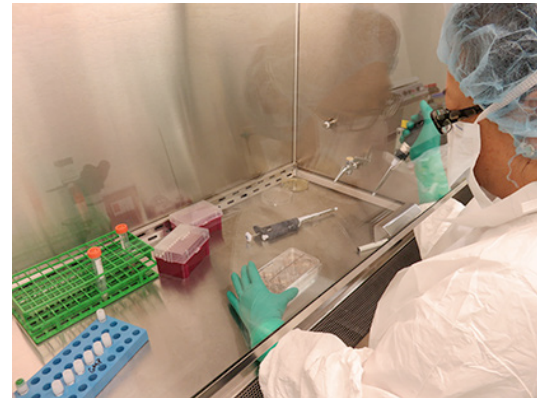
Credit: Joan Brugge, Ph.D., Harvard Medical School

As researchers develop new approaches to overcoming tumor avoidance of immune destruction and new methods for identifying antigens on tumor cells that can be targeted most effectively, immunotherapy is becoming an integral part of precision medicine. NCI continues to support many grantees and intramural investigators working to treat cancers with immunotherapy, including:

- inhibitors of immune checkpoint molecules (proteins that normally limit the strength of immune responses to prevent damage to normal tissues)
- immune cell therapy (adoptive T-cell transfer and chimeric antigen receptor T-cell therapy)
- therapeutic antibodies (antibodies linked to toxic substances and antibodies that partner with immune cells to kill cancer cells through a process known as antibody-dependent cell-mediated cytotoxicity)
- immune modifying agents (cytokines and growth factors)
- therapeutic vaccines that elicit immune responses against normal (i.e., nonmutant) antigens that are highly expressed by cancer cells or “neoantigens” that are generated by mutation during tumor development

Although many patients are deriving benefit from immunotherapy, research is still needed to:

- increase our understanding of what enables this approach to work in some patients but not in others who have the same cancer
- find ways of expanding the use of immunotherapy to more types of cancer
- better understand how to use immunotherapies in combination with targeted therapies and standard treatments, such as chemotherapy and radiation therapy



Michelle Becker-Hapak, a research lab supervisor at Washington University School of Medicine in St. Louis, works on a personalized melanoma vaccine.

Credit: National Cancer Institute

Strategies for the Prevention and Early Detection of Cancer

The prevention of cancer and the development of more effective strategies to detect cancer precursors and early-stage cancers, when treatment may be most effective, remain critical goals.

Although the pharmaceutical industry regularly funds diagnostic and treatment research, the majority of prevention research is funded by the public sector. This is because preventive agents and interventions provide minimal or no potential for commercial profit.

Nevertheless, prevention has the potential to save more lives from cancer than treatment and spares individuals the physical and psychological morbidity caused by cancer diagnosis and treatment. For these reasons, strong support for this area of research is important.

Preventing Cancer Caused by Viral Infections

Identifying infectious agents that cause cancer provides several paths to prevention, including reduction or elimination of exposure to the agent, developing a vaccine that prevents infection, or treating the infection before cancer develops.

Recent developments for three oncogenic viruses—human papillomavirus (HPV), Epstein-Barr virus (EBV), and hepatitis C virus (HCV)—illustrate how research advances have the potential to substantially reduce cancers attributable to these agents.

Further NCI-funded research aims to:

- confirm whether administering fewer than the recommended three doses of FDA-approved HPV vaccines will provide long-term protection against HPV-associated cancers
- determine whether treating high-grade anal dysplasia, which is associated with HPV infection, can reduce the likelihood of invasive anal cancer
- increase the accuracy and efficiency of cervical screening tests
- aid in the development of a prophylactic vaccine against EBV infection, which is thought to account for more than 200,000 new cases of cancer each year worldwide
- develop a prophylactic vaccine against infection with HCV, which is a major cause of liver cancer

Preventing Cancer with Drugs

NCI has investigated many natural and synthetic compounds to see if they have chemopreventive properties—properties that help reduce the risk of various types of cancer. The two most notable successes arising from this research are the approvals by the FDA of the drugs tamoxifen (Nolvadex®) and raloxifene (Evista®) to reduce the risk of breast cancer in women at increased risk of the disease.

Research has indicated that regular aspirin use may be associated with reduced risks of death for several types of cancer, with the

greatest benefit observed for gastrointestinal cancers. Currently, NCI is collaborating with the National Institute on Aging on a 5-year study of aspirin's cancer preventive benefits and side effects, in hopes of providing information that will better guide the use of aspirin for chemoprevention.

Long-term chemoprevention of cancer with aspirin has been limited by concerns about side effects. Genomics and precision medicine may enable identification of individuals who are most likely to benefit from the use of aspirin or other chemopreventive agents, those who will not, and those who may actually be harmed by these interventions.

Consequently, NCI is supporting research in this area. One example is a recent study, funded largely by NCI, in which participants who carried specific genetic variants were found to have reduced risks of colorectal cancer with regular aspirin and/or nonsteroidal anti-inflammatory drug (NSAID) use, whereas participants with other genetic variants had increased risks of the disease.

Identifying New Biomarkers for Risk and Early Detection of Cancer

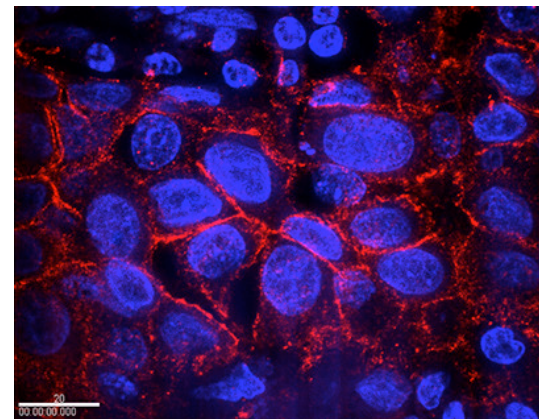
Discovering biological markers, or biomarkers, that can accurately identify people at increased risk of cancer or who have early cancers provides opportunities for medical intervention to reduce risk, for ongoing surveillance and deferral of treatment until necessary, or for early intervention when cancer therapy may be most effective.

Our ever-increasing understanding of the mechanisms of cancer, greatly facilitated by advanced genomic, proteomic, and other molecular technologies, is amplifying opportunities for cancer biomarker discovery and development. The potential rewards—in terms of cancer cases and deaths avoided—make this an extremely important area of investigation.

Although many candidate cancer biomarkers have been identified in recent years, few have been validated as being clinically useful. Therefore, guidelines and frameworks for the development and validation of biomarkers have recently been developed.

Current research aims to:

- discover and validate biomarkers that can help diagnose cancer at its earliest stages more easily, cheaply, and less invasively
- identify people at increased risk of cancer who may need to be closely monitored for cancer development



Breast cancer cells that overexpress the HER2 biomarker, with the cell nuclei stained blue and the HER2 protein in bright red at the cell membranes. Trastuzumab (Herceptin®) can be used to treat cancers that overexpress HER2.

Credit: National Institute of Standards and Technology

- identify biomarkers that can discriminate between life-threatening cancers and cancers that will not cause symptoms or threaten life and between precancerous growths that will progress to invasive cancer and those that will not
- correlate findings from studies testing various imaging modalities for the early detection of cancer with similar biomarker studies

Examples of biomarkers currently being developed include tumor DNA and cancer cell exosomes (membrane-enclosed cell fragments that contain proteins, DNA, and RNA) shed into the blood.

The Biology of Cancer Health Disparities

Cancer health disparities, differences in cancer incidence and outcomes among different racial and ethnic groups, are thought to reflect the interplay of socioeconomic factors, culture, diet, stress, the environment, and biology.

The least understood of these factors is the role of biology. But with advanced genomics and other molecular technologies and the growing sophistication of computational tools, understanding how biology contributes to health disparities may finally be within reach.

Until fairly recently, a major barrier to research on the role of biology in cancer health disparities was the lack of large samples of DNA from individuals across a wide range of racial and ethnic groups. Supporting ongoing efforts to build large repositories of samples and data for this research remains a priority.

NCI currently supports a broad range of research aimed at identifying and understanding biological differences in cancers that arise among different racial and ethnic populations, and how biological factors interplay with other factors, such as diet and the environment, in contributing to cancer health disparities.

Examples include research to identify:

- genetic mechanisms that explain the biological differences between triple-negative breast cancers that arise in African American women and those that arise in women of other racial and ethnic groups
- genetic mutations that appear to be preferentially associated with colorectal cancers that arise in African American men and women compared with white men and women

- genetic variations that may explain the higher risk of prostate cancer among African American men compared with white men
- epigenetic differences and differences in gene expression patterns and other molecular characteristics that may explain differences in the aggressiveness of prostate cancers between African American men and white men

As our understanding of the role biology plays in cancer health disparities grows, new opportunities for prevention, early detection, and intervention will undoubtedly be revealed. However, as a society, we must also continue to explore innovative ways to mitigate the effects of nonbiological factors that contribute to cancer health disparities, such as limited access to and use of health care services, including cancer screening programs, and the ability to pay for care.



Melanie Nix is a survivor of triple-negative breast cancer.

Credit: National Cancer Institute