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DIRECTOR’S MESSAGE: BUILDING ON SUCCESS, MAXIMIZING OPPORTUNITIES

The year 2021 will mark the 50th anniversary of the National Cancer Act of 1971, the landmark legislation that intensified support for cancer research in the United States. The investment sparked a biomedical revolution that has led to extraordinary progress in our understanding of the causes of cancer and its progression, as well as in our ability to prevent, diagnose, and treat the disease.

Over the last 5 decades, mortality rates have declined for most cancers, largely due to improvements in prevention, detection, and treatment. These advances have been fueled by breakthrough studies of complex environmental and genetic interactions that can lead to cancer, the identification of targets that drive cancer, and the development of effective interventions against those targets.

We have been able to make these strides thanks to continuing congressional support for NCI and strong engagement from academic, advocacy, patient, nonprofit, and commercial sectors. And additional funds provided through the Cancer Moonshot℠ beginning in fiscal year (FY) 2017 are serving as a catalyst for further progress.

Nonetheless, cancer remains a formidable problem, and too many patients with cancer still face a grim prognosis. Each minute in the United States, more than three people are diagnosed with the disease and approximately one person dies from it. In addition, survivors can face serious cancer-related health issues.

Researchers grapple with many unanswered questions: Why do many cancers initially respond to therapy and later become resistant? How can we reduce serious long-term side effects for survivors of childhood and adult cancers? How can we ensure that high-quality cancer care is available to all who need it?

Meeting these and myriad other challenges requires sustained and robust investment in all areas of cancer research, from exploration of the causes and biological mechanisms of cancer to prevention, detection, treatment, and survivorship.

NCI’s research strategy includes supporting investigator-initiated research and maximizing opportunities in emerging areas of science. The Annual Plan & Budget Proposal for Fiscal Year 2021 focuses on three emerging areas: the immune system and microbiome, artificial intelligence, and implementation science. There are many more areas that need to be addressed as well.
Our investments must not only support cutting-edge research but also strengthen the infrastructure that enables innovation and trains a diverse and talented workforce for the important work ahead.

An unprecedented enthusiasm has permeated the research community. We are buoyed by the explosion of new research ideas, as evidenced by a 50% increase in grant applications to NCI over the past 5 years and the extraordinary number of new cancer drug approvals, which offer more options and hope to patients.

But if our budgets are unable to meet the pace of this growing interest and enthusiasm, we will be confronted with a serious challenge. If discouraged researchers leave the field, we will squander the tremendous momentum and innovation alive in the research community today. There can be no pause button for cancer research.

Today’s investments lay the foundation for tomorrow’s breakthroughs, just as today’s advances were built on earlier discoveries made since the National Cancer Act was signed into law. We must intensify our pursuit of better outcomes for patients and their loved ones. We owe them nothing less. The NCI Annual Plan & Budget Proposal lays out how.

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

Increase in NCI R01 Grant Applications Outpacing NCI Budget

* Applications for FY 2013–2018 are from NIH RePORT, FY 2019 is based on the number of applications received to date, and FY 2020–2021 applications are modeled based on the rate of growth between FY 2018–2019

† NCI budget shown is the base appropriation and does not include Cancer Moonshot funding
Immensely opportunities exist in cancer research along the continuum from basic research to survivorship. This budget proposal for FY 2021 includes investments in six areas needed to advance progress in cancer as well as support for the infrastructure and training that enables cutting-edge research to succeed.

The budget proposal also includes $50 million for the Childhood Cancer Data Initiative as well as Cancer MoonshotSM funding, which was authorized in the 21st Century Cures Act. Cancer Moonshot funding ends in FY 2023.

Included in this investment is a substantial increase to the budget for R01 research project grants, one of the main ways NCI supports investigator-initiated science.

The increase in high-quality research applications has far outpaced the NCI budget and our ability to fund them at an acceptable success rate. The FY 2018 success rate for NCI applications was 12%, while the rate for the rest of NIH was 22%.

The budget proposal for FY 2021 would give NCI the flexibility to begin improving the payline for R01 grants from the current 8th percentile to the 15th. This would enable funding for additional meritorious research proposals and allow us to act on more opportunities to prevent, detect, and treat cancer.

Paylines & Success Rates for NCI R01 Applications Remain Low

Payline is the preset funding cutoff point used to fund unsolicited grants (Source: NCI Budget Fact Book)

Success rate is the percentage of peer-reviewed grant applications that receive funding (Source: NCI Funding Patterns)
## PROFESSIONAL JUDGMENT BUDGET PROPOSAL FOR FY 2021

(dollars in millions)

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<tr>
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<th>FY 2021 Base Budget Proposal</th>
<th>FY 2021 Cancer Moonshot™ Funding</th>
<th>FY 2021 Total</th>
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<tr>
<td><strong>FISCAL YEAR 2019 NCI Base Appropriation</strong></td>
<td>$5,744</td>
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<td>$6,928</td>
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<tr>
<td><strong>Total Budget Increase Proposed Allocation</strong></td>
<td>$989</td>
<td>$195</td>
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<td></td>
<td>$314 Inflation Adjustment‡</td>
<td>$105 Detecting &amp; Diagnosing Cancer</td>
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<tr>
<td></td>
<td>$115 Understanding Cancer</td>
<td>$180 Preventing Cancer</td>
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<td>$180 Preventing Cancer</td>
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<td>$115 Understanding Cancer</td>
<td>$65 Advancing Public Health in Cancer</td>
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<td>$30 Training &amp; Infrastructure</td>
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‡ Adjustment includes inflation for the 2 years between FY 2019 and FY 2021

§ In addition to the inflation adjustment, the increase of $989 million includes $50 million for the Childhood Cancer Data Initiative and $625 million for additional cancer research in six areas
Leading the Nation’s Progress against Cancer

The National Cancer Institute’s mission is to lead, conduct, and support cancer research across the nation and around the world to advance scientific knowledge and help all people live longer, healthier lives. In advancing this mission, NCI is the world’s largest funder of cancer research and manages a broad range of associated activities, including training, information dissemination, and infrastructure and resource development for cancer research and patient care.

The Return on Cancer Research Investment

NCI collects and analyzes data to generate statistics on cancer incidence, mortality, and survivorship, so trends in the burden of cancer among Americans can be measured. As examples of this progress, the most recent statistics show that:

- **The overall rate of cancer deaths in the United States declined steadily for more than two decades.** From 1991 through 2016, the age-adjusted rate of death for all cancers combined fell by more than 27%. In 2017 alone (the most recent year for which statistics are available), the age-adjusted rate of death from cancer was 2.1% lower than it was in 2016.

- **From 2007 through 2016, the rate of new cancer cases fell by 1.5% 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

Shrinking a Tumor, Changing a Life

When Rihanna was born, her parents and doctors were alarmed to see a large mass on her upper right arm. A routine prenatal ultrasound only 10 days earlier had shown nothing out of the ordinary. Rihanna was diagnosed with a rare cancer known as infantile fibrosarcoma. The medical teams responded quickly by putting her on a course of intensive chemotherapy. After 4 months of treatment, her tumor had not shrunk.

At 5 months of age, baby Rihanna was facing possible amputation of her arm when she was referred to Memorial Sloan Kettering Cancer Center. She was enrolled in an NCI-funded clinical trial of larotrectinib (Vitrakvi), a drug that targets TRK fusions, a mutation characteristic of her tumor. NCI scientists first identified TRK fusions, which, although rare, are expressed in multiple types of cancer in children and adults.

Rihanna’s mother, Ana, recalls, “She started the drug on a Monday, and, by Wednesday, I already saw the tumor shrinking like a raisin. She had no side effects.” Larotrectinib therapy allowed the surgeons to remove the mass without compromising function of her arm. Rihanna underwent 2 years of treatment, and now at 2.5 years old, she remains cancer free and no longer needs the drug. Her parents are thrilled to see their little girl light up the room with her charismatic personality.

Thanks to NCI-funded research, Rihanna is a happy and healthy toddler. Discussing the now Food and Drug Administration-approved drug, Ana reflected, “I’m excited that Rihanna’s experience with larotrectinib has helped give other people the opportunity for a full and healthy life, too.”
incidence has not been equivalent for men and women. From 2007 through 2016, the rate of new cancers cases declined for men but was stable for women.

- The incidence and mortality rates for several cancer types fell significantly over time. These improvements varied by sex and race/ethnicity, with notably greater improvement among minorities compared with whites for certain forms of cancer. For example, the greatest declines in lung and bronchial cancer incidence from 2007 through 2016 were observed among Hispanic males and black females, with declines 17% and 6% larger than those observed among white males and females, respectively. During the same period, the greatest declines in lung and bronchial cancer mortality were observed among black males and black and American Indian/Alaska Native females (tied), with declines 17% and 12.5% larger than those observed among white males and females, respectively.

- From 2007 through 2016, the greatest declines in cancer incidence and mortality were observed among blacks compared with other racial and ethnic groups. In spite of this, cancer mortality remains highest among blacks. From 2012 through 2016, cancer mortality was 15% higher among blacks than among whites.

The Need for Greater Progress

Advances in detecting and diagnosing certain cancers at an early stage, improvements in treatment, and public health initiatives that encourage people to adopt proven cancer prevention and screening strategies have all contributed to the progress made against cancer to date. Yet, progress in preventing, diagnosing, and treating cancer is not uniform for all types of the disease. The death rates for some cancers, such as bladder cancer, have not declined, and rates for others, such as liver cancer, have increased.

There is still much work to do. The challenges that lie before us are once again reflected in the most recent cancer statistics:

- Too many people are still diagnosed with cancer and die from it. It is estimated that more than 1.7 million adults in the United States will be diagnosed with cancer in 2019, and more than 600,000 will die from it—more than one person every minute. In addition, more than 16,000 new cases of cancer and nearly 1,800 cancer deaths will occur among children and adolescents in the United States in 2019. Furthermore, as the population ages, the numbers of new cancer cases and deaths among adults will continue to grow, even if the age-adjusted incidence does not go up.

- Too many cancers are still not preventable, readily detectable, or curable. Several deadly types of cancer, including pancreatic, ovarian, and kidney cancers, are often diagnosed at late stages because they do not cause early symptoms, and screening tests to detect them early do not exist. Current treatments for some cancer types, including sarcomas, glioblastoma, and liver and pancreatic cancer are not very effective. Progress against all cancers that affect children and adolescents is urgently needed. The Cancer Moonshot℠ is supporting this critical need, including uncovering the mechanisms governing how fusion oncoproteins drive childhood cancers to facilitate drug discovery. Several childhood cancers driven by fusion oncoproteins, such as Ewing sarcomas and fibrolamellar carcinoma.
US Cancer Deaths Averted in Men & Women from 1991 to 2016

OBSERVED CANCER DEATHS
PROJECTED CANCER DEATHS

*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.

Source: Data provided by the American Cancer Society, Inc.
(a type of liver cancer), are in need of effective therapies.

• **All people do not benefit equally from research advances.** Specific populations in the United States, including certain racial/ethnic groups and rural populations, suffer disproportionately from some cancers. Two factors that may contribute to these disparities are inadequate access to cancer screening tests and inadequate access to quality cancer care. Research indicates that genetics, modifiable risk factors, and environmental exposures are also important. More research is needed to better understand and mitigate the effects of both biological and nonbiological factors that contribute to cancer disparities.

• **Declining cancer mortality means the number of survivors and the challenges they face will continue to grow.** In January 2019, it was estimated that there are 16.9 million cancer survivors in the United States. This number, which represents 5% of the US population, is projected to increase by 28%, to 21.7 million, by 2029. Unfortunately, cancer survivors often face numerous challenges following successful treatment. For example, they have an increased risk of developing a second cancer, other serious health conditions, or both. Survivors of childhood cancers, on average, will have to cope with these effects for much longer periods of time than adult survivors. The needs of cancer survivors require greater attention to ensure that they have the best possible quality of life.

• **Cancer is a growing global health burden. Improvements in nutrition, health care, and other factors are increasing life expectancy for most of the world.** However, this benefit is accompanied by higher rates of many diseases associated with aging, including cancer. This negative trend is being exacerbated by greater tobacco consumption in many low- and middle-income countries. Worldwide, more than 27 million new cases of cancer are predicted to occur in 2040, an increase of 50% over the 18 million cases that occurred in 2018. It is also predicted that more than 16 million cancer-related deaths will occur in 2040, an increase of 60% over the nearly 10 million cancer-related deaths reported in 2018.

## Recent Advances in Cancer Research

Every year, NCI-supported scientists in the United States and around the world publish their latest research findings in peer-reviewed biomedical journals. Improving the prevention, diagnosis, and treatment of cancer depends on many kinds of science, including basic, preclinical, clinical, and population research.

Advances in cancer research are also cumulative. Today’s investments in basic science will lay the foundation for tomorrow’s advances in clinical research—just as many of today’s advances were built on discoveries made many years ago.

Recent examples of NCI-supported research advances are highlighted on the pages that follow.
Today’s investments in basic science will lay the foundation for tomorrow’s advances in clinical research.

Understanding the Mechanisms of Cancer

• **Learning how melanoma cells escape immune destruction:** A research team led by scientists at the University of Pennsylvania recently demonstrated that melanoma cells continuously shed small vesicles, called exosomes, that are coated with a protein called PD-L1. When this exosomal PD-L1 binds to a protein called PD-1 on the surface of immune cells known as cytotoxic T cells, the T cells become inactivated, thereby preventing them from destroying melanoma tumors. The researchers also showed that measuring the level of exosomal PD-L1 in the blood may help identify patients who are less likely to respond to drugs that boost immune responses by blocking the interaction of PD-L1 and PD-1.

• **Developing a new strategy to treat pancreatic cancer:** Nearly all pancreatic cancers are driven by mutated proteins called RAS. However, treatments that directly inactivate these mutant proteins are lacking. Recently, research teams at the University of Utah and the University of North Carolina at Chapel Hill independently showed that blocking the activity of proteins downstream from RAS induces a cell-survival process called autophagy. During autophagy, cells actively recycle proteins and other components to continue growing under conditions of stress. The researchers showed that disrupting RAS signaling while, at the same time, inhibiting autophagy with the drug chloroquine blocked the growth of pancreatic cells in the laboratory and caused human pancreatic tumors in mice to shrink. This approach may represent a new treatment strategy for pancreatic and other RAS-driven cancers. New research advances hold promise for directly targeting RAS in the future.

Effective point-of-care cervical cancer screening might become achievable worldwide using contemporary digital cameras.

• **Preventing prostate cancer with finasteride:** Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among US men. In 1994, NCI launched the Prostate Cancer Prevention Trial (PCPT) to determine whether the drug finasteride could reduce the incidence of prostate cancer in men aged 55 and older. Initial results from the trial, published in 2003, indicated that finasteride could reduce the overall incidence of prostate cancer by 25% but that it might also increase the risk of high-grade tumors. The initial concern about high-grade tumors was recently shown to be unwarranted. After a median follow-up of 18.4 years, PCPT researchers have reported that finasteride reduced the number of prostate cancer deaths among the trial participants by 25%.
Detecting and Diagnosing Cancer

- **Analyzing tumor DNA in urine to detect bladder cancer recurrence:** After treatment for localized bladder cancer, patients usually undergo cystoscopy (examination of the lining of the bladder) and urine cytology (looking for cancer cells in urine) to monitor for disease recurrence. However, cystoscopy is invasive, and urine cytology can be inaccurate. Recently, a team of scientists led by researchers at Stanford University reported the development of uCAPP-Seq, a new method to detect bladder tumor DNA in urine. uCAPP-Seq accurately detected tumor DNA in the pretreatment urine samples of patients with early-stage bladder cancer and post-treatment urine samples of patients whose cancers later recurred. When used to monitor a patient’s condition after treatment, uCAPP-Seq significantly outperformed cystoscopy and urine cytology combined in detecting recurrent disease.

- **Diagnosing lymphoma with an automated portable device:** The high prevalence of AIDS-related cancers, including diffuse large B-cell lymphoma and Burkitt lymphoma, in sub-Saharan Africa is a major health challenge. Accurately diagnosing and treating these aggressive B-cell lymphomas is often hampered by limited resources for tissue collection and analysis and limited availability of health care specialists. Recently, a research team led by scientists at Massachusetts General Hospital developed a portable, automated, low-cost point-of-care device that can accurately diagnose B-cell lymphomas. The device captures B cells in biopsy specimens, “immunostains” the cells with specific antibodies, and then subjects them to holography (a photographic technique that records light scattered from an object and presents it as a 3D image). The holographic pattern of stained lymphoma cells differs from that of unstained cells, and artificial intelligence is used to analyze the images. The device yields quantitative readouts of malignant cell number, cell size, and differentiation between high- and low-grade subtypes based on biomarkers. This device can be used to distinguish benign growths from lymphomas and to classify lymphomas into those that require prompt chemotherapy and those that do not.

Treating Cancer

- **Introducing a new treatment for hairy cell leukemia:** Hairy cell leukemia (HCL) is a type of chronic B-cell leukemia named for the hair-like projections found on their cell surfaces. Although many patients can achieve long-term complete remission with the drugs pentostatin (Nipent) and cladribine, about half of patients will relapse within 16 years and require additional treatment. Therefore, therapies that provide durable complete responses and fewer side effects for patients with relapsed or refractory HCL are needed. Recently, an international research team reported positive results from a clinical trial that tested the immunotoxin (an antibody linked to a bacterial toxin) moxetumomab pasudotox (Lumoxiti) in patients with relapsed or refractory HCL. The immunotoxin, which was developed in NCI’s intramural research program, induced a high rate of durable responses and eliminated detectable disease with acceptable side effects. This finding led the Food and Drug Administration (FDA) to approve moxetumomab pasudotox as a treatment for relapsed or refractory HCL.

- **Targeting a genetic abnormality with larotrectinib:** Gene fusions involving NTRK genes, which encode proteins called tropomyosin receptor kinases (TRKs), are found in a variety of adult and childhood cancers. The resulting hybrid genes produce proteins, called fusion oncoproteins, that drive tumor growth. An international team of researchers recently reported findings from three early-phase clinical trials, supported in part by NCI, that showed the drug larotrectinib (Vitrakvi) induced lasting responses in patients with 17 different types of cancer whose tumors were positive for an NTRK gene fusion. The overall response rate with
larotrectinib, including complete responses, partial responses, and stable disease, was 75%. Seventy-one percent of the responses lasted at least one year. Based on these results, larotrectinib was approved by FDA in 2018.

*NTRK* gene fusions were first discovered by scientists in NCI’s intramural research program in the mid-1980s. Read how Rihanna from Connecticut benefited from this drug on page 7.

**NTRK gene fusions were first discovered by scientists in NCI’s intramural research program.**

### Advancing Public Health in Cancer

- **Addressing rural–urban disparities in cancer outcomes:** Approximately 20% of the US population diagnosed with cancer lives in rural areas, and research has shown that rural patients have worse cancer outcomes overall than urban patients. However, NCI-supported researchers recently reported that rural and urban patients who had uniform access to high-quality care through participation in a clinical trial had similar cancer outcomes. The study compared the outcomes of rural and urban patients treated for cancer in clinical trials conducted by SWOG, a National Clinical Trials Network trial group and NCI Community Oncology Research Program research base, from January 1, 1986, through December 31, 2012. These findings suggest that expanding access to high-quality cancer care may help resolve the disparity in cancer outcomes between rural and urban patients.

- **Launching BRCA Exchange to inform our understanding of cancer risk:** NCI recently launched a publicly available online resource called the BRCA Exchange, which contains aggregated information from around the world on thousands of inherited variants of the *BRCA1* and *BRCA2* genes. Researchers have known for many years that certain variants in these genes increase the risk of breast, ovarian, and other cancers, whereas other variants are not associated with disease or are of unknown significance. Physicians and patients need to know whether a given variant is likely to be pathogenic (associated with disease) and how likely a pathogenic variant will cause cancer (the variant’s penetrance). Until now, the data on inherited variants in these genes were not cataloged in a comprehensive manner. The BRCA Exchange demonstrates that comprehensive data sharing is possible, and it could serve as a model for sharing data on other cancer predisposition genes or genes associated with other diseases.
Tomi—North Carolina
Associate Professor, Duke University
Envisioning the Future of Cancer

roundbreaking improvements in treatment and prevention have led to a 27% decrease in cancer mortality in the United States over the past 25 years. These improvements are the result of the critical investments our country has made in cancer research.

More recent discoveries across multiple disciplines are fueling new paradigms that were once unimaginable, such as:

- Therapies that unleash the power of a person’s immune system to attack their cancer
- Agents that target previously “undruggable” proteins driving cancer development and growth
- Noninvasive molecular tests to detect precancers and early cancers
- Vaccines to prevent cancers not associated with infection

Despite this progress, too many cancers are not prevented, detected early, or treated successfully. In addition, cancer survivors often suffer a diminished quality of life due to the harmful effects of their treatment and are at risk of another cancer. Although more research is needed to fully address these issues, more can be done right now to reduce the burden of cancer further by better implementing known and effective cancer prevention, screening, and treatment strategies.

Recent discoveries across multiple disciplines are fueling new paradigms that were once unimaginable.

We know that cancer is not one disease but many hundreds of diseases. Continued progress can be achieved through NCI’s overarching strategy of supporting a broad portfolio of research, which includes further investigation of the basic biological mechanisms of cancer, translating the

Striving to Eliminate Ovarian Cancer Disparities

Tomi Akinyemiju, Ph.D., an epidemiologist studying disparities in ovarian cancer, wants patients to have equal access to quality treatment. Her global background—born in the United States but with much of her youth spent in Africa—is one of the factors that led her to focus on cancer disparities research. To eliminate racial differences in survival, “we need to ensure all women with ovarian cancer have access to and benefit from the best first-line treatments available, regardless of their race,” she says.

Tomi received an R01 grant from NCI on her first submission and was thrilled to learn a week later that it would be converted to an NCI ESI MERIT R37 award. The R37 award allows eligible early-stage investigators like Tomi the opportunity for a 2-year extension of additional support beyond the typical 5 years for an R01 grant.

Her research aims to help predict why women of different population groups are less likely to receive high-quality ovarian cancer treatment. Tomi believes that racial differences in access are not simply about socioeconomic status. They also involve patient–doctor relationships built on trust, access to hospitals and medical centers that specialize in treating cancer, and other factors. Tomi is grateful for the opportunity of the additional years of research support, which she will put to good use trying to help women with ovarian cancer.
knowledge gained into new tools and treatments, and disseminating those innovations into clinical practice.

The three topics discussed in depth in this Annual Plan and Budget Proposal—the immune system and microbiome on page 25, artificial intelligence on page 33, and implementation science on page 39—are just a few of the many exciting areas of opportunity in cancer research.

Tackling the problem of cancer from many different angles will enable a future where:

- Researchers have a comprehensive understanding of cancer biology that catalyzes the development of new ways to prevent, detect, diagnose, and treat cancer
- More cancers are prevented because a person’s cancer risk will be known and reduced effectively
- Fewer people suffer and die from cancer because the disease and its precursors can be detected and diagnosed at the earliest possible stage
- All patients with cancer have safe and effective treatments
- All population groups benefit equally from advances in cancer research

This vision can only be achieved with robust and sustained support for cancer research, allowing investigators across the country to pursue their most innovative ideas in all areas of science. Long-term investments in cancer research will help all people live longer, healthier lives.

Understanding the Mechanisms of Cancer

Virtually all major advances against cancer originated with discoveries in the basic sciences. Basic research reveals new concepts about the causes of cancer and how it develops, progresses, and responds to therapy. This knowledge is essential for finding new ways to prevent, detect, and treat the disease.
NCI’s support of basic cancer research is critical. Long-term investments in research without immediate clinical application are not typically made by industry. One of the main ways NCI supports basic cancer research is through peer-reviewed research project grants, which fund most investigator-initiated science.

**Virtually all major advances against cancer originated with discoveries in the basic sciences.**

The return on NCI’s sustained investment in basic scientific research has been remarkable. For example, more than 40 years ago, scientists studying how retroviruses cause cancer discovered the first human oncogene (a gene that can transform a normal cell into a cancer cell). This novel and unexpected insight into cancer development, and other insights that followed, opened previously unexplored areas of cancer biology—ultimately leading to a new era of precision oncology and new approaches for cancer prevention, detection, and treatment.

Similarly, NCI-supported scientists investigating how immune responses are regulated applied their findings to unleash the power of the immune system to attack cancer, thus leading to many of the immunotherapies available today.

With the creativity of NCI-funded researchers and innovative new technologies, what new insights will be possible in the future? What additional, unsuspected causes of cancer might be discovered? What fundamental findings in cancer biology will lead to the next cancer treatment breakthrough? What new technology might be developed that revolutionizes cancer research?

The knowledge gained from our investments in basic research will drive 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**

To improve our understanding of the many diseases we call cancer, we must unravel the complexity of how normal cells become cancerous and how cancer cells grow, survive, and spread throughout the body. To do this, NCI is focused on the following goals:

1. **Develop a Comprehensive Understanding of the Molecular and Cellular Basis of Cancer**

A more complete understanding of cancer cell biology will enable new prevention, detection, and treatment approaches, which take advantage of vulnerabilities identified in cancer cells and their precursor lesions. Major objectives are to:

   - Understand the genetic changes that give rise to cancer, as well as how genes are abnormally regulated (e.g., epigenetics)
   - Identify how tumors evolve and respond to or resist treatment
   - Study how cellular processes—such as cancer cell metabolism, stress responses, and cell-cycle regulation—contribute to cancer development and progression

2. **Understand How Cancer Cells Interact with Normal Cells in the Body to Support or Suppress Tumor Development and Progression**

Cancer can start in almost any tissue in the body, and the tissue in which a cancer arises and spreads can influence its molecular characteristics. This illustrates the importance of understanding the interactions between cancer cells and the surrounding normal cells to develop new prevention and treatment approaches. Major objectives are to:

   - Characterize the components of the tumor microenvironment—including the cancer cells, connective tissue cells (fibroblasts), immune cells, bacterial cells (the tumor microbiome),
blood vessels, and nerves—and determine their individual and collective influences on tumor progression and regression

- Understand the mechanisms by which cancer cells communicate with surrounding normal cells and enlist their help in promoting tumor growth
- Elucidate how cells and tissues in other parts of the body interact with cancer cells to prevent or promote metastasis (spread)

**Preventing Cancer**

Prevention research, supported by NCI and others, has contributed to the decline in the overall rate of cancer incidence seen in the United States during the last 25 years.

NCI’s commitment to funding cancer prevention research is especially important because the private sector is hesitant to conduct such research due to the many economic, scientific, logistical, regulatory, and legal considerations that must be addressed.

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 (Evista) can reduce the risk of breast cancer in women at increased risk of the disease; and the development of human papillomavirus (HPV) vaccines to prevent the majority of cervical, vaginal, vulvar, anal, rectal, oropharyngeal (throat), and penile cancers.

**NCI funding has supported major advances in cancer prevention.**

Major opportunities in cancer prevention are before us. For example, discoveries made in cancer biology, immunology, and vaccine science are using the power of the immune system to prevent cancers that are not caused by infectious agents, which represent the vast majority of new cancer cases.

In the future it will be possible to vaccinate individuals at high risk of certain cancers, such as those with inherited cancer predisposition syndromes, training their immune systems to protect them against cancer development.

Strong investments in cancer prevention research by NCI will mean a future with lower cancer incidence and morbidity. In other words, fewer people will have to face the physical, financial, social, and psychological harms of a cancer diagnosis and treatment.

**Strong investments in cancer prevention research by NCI will mean a future with lower cancer incidence and morbidity.**

**Vision**

*More cancers will be prevented because a person’s cancer risk will be known and reduced effectively.*

**Approach**

Just as we are increasingly able to identify the best treatments for a person’s cancer based on the genetic abnormalities of their tumor, understanding a person’s genetic risk factors and environmental exposures over time should enable us to tailor personalized measures to prevent cancer. This future can be realized by supporting the following goals:

1. **Identify and characterize risk factors for cancer**

   Opportunities exist to identify genetic and environmental risk factors for cancer, in addition to those already known, and to understand how genes and the environment interact to influence cancer risk. Major objectives are to:

   - Characterize the biology of precancerous lesions and their progression to cancer, including molecular signatures, or “fingerprints,” of the DNA damage and repair processes the cancer cells and their precursors have experienced
• Develop more-precise individualized assessments of cancer risk, allowing people at increased risk to receive the most appropriate medical care to manage that risk

2. Develop and Test New Approaches for Cancer Prevention

NCI is committed to discovering new cancer prevention approaches, including strategies based on an increased understanding of biological and behavioral factors. Major objectives are to:

• Develop and test new strategies to further reduce the impact of modifiable risk factors for cancer, such as unhealthy lifestyle choices

• Support research to fully leverage the immune system to prevent cancer (immunoprevention), including cancers caused by infectious agents and those that are not

• Identify new chemical agents or repurpose existing agents to prevent cancer (chemoprevention)

Detecting and Diagnosing Cancer

Cancer detection and diagnosis involve identifying the presence of cancer in the body and assessing the extent of disease—whether it is the initial diagnosis of a cancer or the detection of a recurrence. For some cancers, this definition can be expanded to include identifying precancerous abnormalities that are likely to become cancer, providing an opportunity for early intervention and preventing cancer altogether.

NCI funding has contributed to many major advances in cancer detection and diagnosis. For example, in 1979, NCI-supported research established the effectiveness of screening mammography for detecting early-stage breast cancer. In addition, NCI-sponsored studies demonstrated the effectiveness of lung cancer screening with low-dose computed tomography in reducing lung cancer mortality in 2011 and led to the first Food and Drug Administration (FDA) approval of an HPV test for cervical screening in 2014.

NCI-funded research is fueling innovative new technologies that will change cancer detection and screening in the future. Someday, a simple blood draw (a liquid biopsy) in a doctor’s office may be used to detect, diagnose, and monitor many types of cancer. In addition, imaging technologies coupled with artificial intelligence may be able to identify the presence, type, stage, and major genetic features of a cancer without the need for an invasive biopsy.

Someday, a simple blood draw in a doctor’s office may be used to detect, diagnose, and monitor many types of cancers.

Additional research will enable the development of more-sensitive, accurate, and cost-effective methods of detecting, diagnosing, and, in some cases, preventing cancer in the future.

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

Advances in biomedical technologies are enabling the development of new tools for cancer detection and diagnosis. Our goals include the following:

1. Improve Current Methods and Develop New Methods of Detecting Cancer and Its Precursors

NCI’s investments in this area include: developing new or improved detection and diagnosis methods that are more accurate and of greater clinical utility than those available today, and to optimizing the use of proven methods by physicians and health care systems. In addition, producing cost-effective technologies and tests that can be used in all resource settings is essential. Major objectives are to:

• Improve current cancer imaging technologies to enhance their ability to detect cancer or its precursors at the earliest possible stage
• Develop and test new technologies that will enable the identification of cancerous and precancerous cells at the molecular level and provide information about their biological activity
• Find novel ways to combine technologies to enhance cancer detection and diagnosis
• Develop and refine noninvasive tests for the early and accurate detection and diagnosis of cancer

2. Identify and Validate New Biomarkers that Can Be Used for the Early Detection and Diagnosis of Cancer and Its Precursors

The use of tumor biomarkers (e.g., measuring the presence of specific proteins or other molecules in tumor specimens) and imaging biomarkers (e.g., the selective uptake of radioactive substances by tumors visualized through PET scans) is widespread in oncology. NCI’s objectives in developing additional biomarkers are to:

• Identify novel biomarkers, such as changes in cellular metabolites measured in exhaled breath
• Identify and validate new types of blood-based biomarkers, such cell-free DNA fragmentation patterns
• Identify new types of tissue-based biomarkers based on differences in the electrical or mechanical properties of cells or tissues

Treating Cancer

Thanks to NCI-funded research, patients with cancer have a greater number of more-effective and less-toxic therapeutic options today than ever before.

NCI’s support for treatment research extends from investigations of the fundamental mechanisms of cancer, the development of drugs that target those mechanisms, and testing new cancer therapies in clinical trials. NCI also supports critical research infrastructure, including the National Clinical Trials Network (NCTN), which provides robust support for NCI-sponsored diagnosis, treatment, and screening trials.

Breakthroughs in molecularly targeted therapies and immunotherapies have revolutionized the treatment landscape for patients. A better understanding of cancer biology has fueled the development of new classes of drugs, including the first small-molecule molecularly targeted therapy (imatinib [Gleevec]), the first immune checkpoint inhibitor (ipilimumab [Yervoy]), and the first genetically engineered cell-based immunotherapy (tisagenlecleucel [Kymriah]). In 2018 alone, FDA approved 19 new cancer treatments, and NCI-funded research contributed to the development and/or testing of most of them.

Breakthroughs in molecularly targeted therapies and immunotherapies have revolutionized the treatment landscape for patients.

Many more treatment innovations are on the horizon. For example, recent research is creating optimism that, one day, there may be targeted treatments for so-called “undruggable” cancer drivers. These include the oncoproteins RAS and MYC and tumor suppressors such as p53 and PTEN. While clinical testing is needed, the availability of these targeted treatments will be a hallmark of unprecedented progress for patients who have few therapeutic options.

Immense opportunities exist in cancer treatment. One day it will not only be possible to molecularly characterize a patient’s cancer cells, but the cellular composition of their tumor and even the composition of their microbiome will inform treatment decisions. With this information, doctors will select therapies, or combinations of therapies, for each patient—and avoid ones that will have unacceptable side effects. This future will only be possible through additional research investment.

Patients with cancer have a greater number of more-effective and less-toxic therapeutic options today than ever before.
Vision
All patients with cancer will have safe and effective treatments.

Approach
Investing in the opportunities present in cancer research today will further improve the outlook for both adults and children with cancer. Fully realizing the potential to identify, study, and test new cancer therapies requires additional research to achieve the following goals:

1. Discover and Develop New Cancer Treatments, including Those that Involve Moleurally Targeted Therapies and Immunotherapies, as well as Treatment Combinations

Therapies that target the molecular changes in a person’s cancer and immunotherapies that unleash the power of the immune system against the disease are revolutionizing the potential impact of cancer care. Because these newer therapies provide durable clinical benefits to only a small proportion of patients, though, we must develop new therapeutic approaches. Our major objectives are to:

- Identify and characterize new targets for cancer treatment, such as abnormal proteins that are responsible for cancer cell survival, growth, and spread
- Develop new ways to leverage the rapid progress in cancer immunotherapy—including identifying predictive biomarkers, developing novel immune targets, and combining therapies—to benefit more patients
- Understand mechanisms of drug resistance, a major cause of treatment failure in patients, and develop strategies that target these mechanisms, including the use of combination therapies
- Identify and develop additional biomarkers to monitor treatment benefits and harms to aid clinicians in selecting the most appropriate treatments for patients.

2. Improve Traditional Cancer Treatment Approaches, including Surgery, Radiation Therapy, and Chemotherapy

Surgery, radiation therapy, and chemotherapy remain important options for cancer treatment. NCI funds research to improve the effectiveness and utilization of these treatments. We must learn to use them more effectively and minimize their side effects. Our major objectives are to:

- Understand how to combine therapies, including different types of treatment (e.g., radiotherapy with immunotherapy)
- Tailor treatments to avoid overtreatment and unnecessary toxic effects (e.g., de-escalation studies)
- Advance the development of precision radiotherapy to target tumors more specifically and spare the surrounding normal tissue from radiation damage
- Support innovations in cancer surgery, including improving patient selection and approaches to minimize the impact on normal tissue

Advancing Public Health in Cancer

Studying cancer on a population-wide scale yields findings that are used to protect the health of people and their communities. These findings are also used to inform the development and implementation of policies and programs to reduce the burden of cancer. As part of this effort, NCI collaborates with other federal agencies and organizations at the local, state, national, and global levels to support and share evidence-based interventions for cancer control.

NCI-funded research has contributed to major improvements in public health and cancer control. For example, cervical cancer mortality declined 60% in the United States from 1975 through 2016. NCI-supported researchers contributed to technologies such as the Pap and HPV tests, elucidated the cancer-causing nature of HPV, and laid the foundation for the development of the HPV vaccines available today.

In addition, substantial progress has been made in reducing the prevalence of cigarette smoking and its resulting harms since the first
Surgeon General’s Report on smoking and health was published over 50 years ago. In 1964, the prevalence of regular tobacco smoking among adults was 42%. By 2017, it had declined to 14%. Tobacco use is linked to at least 15 cancer types and ending smoking in the United States would eliminate almost one-third of the nation’s cancer deaths.

We are striving to prevent all HPV-associated cancers, eradicate the incidence of cancers caused by tobacco use, dramatically reduce cancer disparities, and see major improvements in the quality of life of cancer survivors in the future. Additional investments in cancer control, population health, and survivorship will continue to reduce cancer risk, incidence, and mortality and improve the lives of cancer survivors and the general population.

Vision
All population groups will benefit equally from advances in cancer research.

Approach
Cancer will continue to grow as a major public health issue in the United States as the population ages. More research and innovation are needed across the entire spectrum of cancer—from prevention to detection and diagnosis to treatment and survivorship—to successfully achieve the following goals:

1. Develop Public Health Interventions to Reduce the Risk of Cancer
It has been estimated that 30%–50% of cancers diagnosed today could be prevented by reducing exposure to tobacco smoke and other environmental carcinogens, maintaining a healthy body weight, and receiving recommended cancer screenings and vaccinations. Identifying innovative ways to help people change their behaviors and make healthy lifestyle choices will have dramatic impacts. Our major objectives are to:

- Further reduce tobacco use among all population groups and better understand the health effects of electronic nicotine delivery devices (e-cigarettes) and alternative tobacco delivery methods (e.g., snus and hookahs)
- Develop informational and behavioral interventions to reduce obesity and reduce the risk of obesity-associated cancers
- Study how physical activity influences cancer incidence and patient outcomes and translate the knowledge gained into effective interventions for individuals at risk, patients undergoing treatment, and survivors who have completed treatment
- Develop interventions to increase the use of proven, effective cancer prevention strategies (e.g., HPV vaccination) and screening methods (e.g., colorectal and lung cancer screening)

Identifying innovative ways to help people change their behaviors and make healthy lifestyle choices will have dramatic impacts.

2. Support Research to Reduce Cancer Disparities
Certain populations, including specific racial/ethnic groups and rural populations, suffer disproportionately from some cancers. The reasons for these disparities include both biological and nonbiological factors. A major nonbiological factor is inadequate access to cancer screening tests, preventive interventions, and high-quality cancer care. Our major objectives are to:

- Develop innovative, portable, low-cost technologies for cancer screening and diagnosis in a doctor’s office, a clinic, or other local care setting
- Develop smoking cessation interventions targeted to socioeconomically disadvantaged populations that could be made scalable for broad population impact
- Evaluate the effectiveness of a single-dose of HPV vaccines and of different formulations of these vaccines, including formulations that do not require refrigeration, to increase HPV
vaccine uptake, especially among medically underserved populations

- Enhance participation of racial/ethnic minorities and the underserved in NCI-sponsored clinical trials

3. Ensure that Cancer Survivors Have the Highest Possible Quality of Life

Many cancer survivors suffer from health problems caused by the disease or its treatment that require additional and, perhaps, ongoing care. Survivors of childhood cancers, on average, will have to deal with these effects for much longer than adult survivors. Our major objectives are to:

- Understand the short- and long-term adverse effects of cancer and its treatment, and develop interventions to reduce their impact on patients

- Identify risk factors, including genetic factors, that contribute to differences between patients in the occurrence and intensity of adverse effects, including the risk of second or recurrent cancers

- Investigate what role, if any, comorbidities (other health problems) play on treatment-related adverse effects so we can more effectively care for the whole patient

- Develop interventions to promote healthy behaviors among cancer survivors to improve both health outcomes and quality of life
Opportunities in Cancer Research: The Immune System & Microbiome

Cancer immunotherapy has emerged as a powerful tool in cancer treatment. The key insight was that a patient’s own immune system could be harnessed to recognize and destroy cancer cells. Thanks to decades of NCI- and NIH-funded basic research, this insight has led to new treatments that have saved or extended the lives of many patients.

Scientists are working diligently to improve current immunotherapy approaches, and promising new areas of opportunity are being identified. For example, researchers are exploring the use of additional types of immune cells as cancer interventions and investigating how microbiomes, the communities of microbes that inhabit the gut and other tissues, shape the immune system and responses to cancer treatment.

Scientists envision this research leading to a future when a patient’s cancer cells, the cellular composition of their tumor, and the status of their immune system and gut microbiome will be molecularly characterized. This information will inform treatment decisions and monitoring of treatment responses. Such a comprehensive analysis of a patient and their cancer may point to combinations of treatments that target multiple factors and offer a better chance for a cure.

Reaching the Stars with a New Immunotherapy Drug

In 2004, Allen’s busy life as a NASA astrophysicist who modeled the evolution of stars was interrupted when he noticed enlarged lymph nodes on the side of his face and jaw. A biopsy revealed lymphoma. “It felt like being hit by a train. My first thought was that I might not see my teenage children grow up,” Allen recalled.

The cancer initially was slow growing but became aggressive in 2012. Combination chemotherapy and an autologous stem cell transplant put it into remission.

Unfortunately, the cancer recurred in 2018. Having run out of standard treatment options, Allen jumped at the chance to join a phase 1 trial at the NIH Clinical Center, one of several sites testing a combination of rituximab (Rituxan) with Hu5F9-G4, a monoclonal antibody that blocks the CD47 protein on tumor cells. This treatment exposes tumor cells to destruction by the immune system. Basic and preclinical research by NCI-funded investigators at Stanford University helped lead to the drug’s development.

Eight weeks after starting treatment, the now-retired Allen felt he had reached the stars again: His scans were negative. “NCI saved my life,” he said. “I never expected to have such a quick response.” Allen is a grandfather now and thrilled to be able to spend more time with his family.

Although Allen’s trial was small, half the patients had a response to the treatment. Given its promising early results, Hu5F9-G4 is progressing in clinical trials for the treatment of multiple types of cancer.
Finding New Ways to Help the Immune System Fight Cancer

Cancer immunotherapy harnesses a patient’s own immune system to recognize and destroy cancer cells. Researchers are exploring how to expand the types of immune cells that can be used for immunotherapy. In addition, scientists are working to better understand how microbes shape the immune system and how they can be used to improve responses to cancer treatment.

Tapping into the Innate Immune System

Most available immunotherapies focus on immune cells called cytotoxic T cells, which are part of the adaptive immune system. Cytotoxic T cells recognize and kill cancer cells that display specific molecules (antigens) on their surfaces. More recently, cancer researchers have turned to the innate, or nonspecific, immune system, seeking to tap its potential for cancer immunotherapy. There are many different types of innate immune cells. The following are just three examples:

**HELPING MACROPHAGES ENGULF CANCER CELLS**

Macrophages are innate immune cells that engulf foreign substances and unhealthy cells such as cancer cells. Some cancer cells express certain proteins on their surfaces that prevent macrophages from engulfing them. Blocking the activity of these proteins enables macrophages to kill cancer cells.

**ENGINEERING NATURAL KILLER CELLS TO TARGET CANCER**

Natural killer (NK) cells are innate immune cells that kill cancer cells by releasing enzymes that form small holes in the cells’ outer surfaces. Researchers are engineering NK cells to express a variety of substances that increase their capacity to kill cancer cells.

**HARNESSING DENDRITIC CELLS TO ACTIVATE T-CELL IMMUNITY**

Researchers are testing ways to exploit dendritic cells, innate immune cells that process antigens and present them to T cells. Researchers are developing different ways to enhance the ability of dendritic cells to prime T cells to attack cancer.
Researchers are investigating whether adding certain gut bacteria, using antibiotics to selectively kill certain bacteria, or modulating the microbiome with diet can improve the effectiveness of immunotherapy.

GUT BACTERIA PLAY A ROLE IN HOW SOME CANCERS START
Certain gut bacteria have been implicated in the development of some types of cancer, such as colorectal cancer. They can cause inflammation and suppress the activity of immune cells, allowing colorectal cancer cells to form and grow.

SOME MICROBES INFLUENCE THE RESPONSE TO CANCER TREATMENT
Researchers have found that some gut bacteria can influence responses to immunotherapy and chemotherapy. Some microbes may modify immune cell activity, whereas others may alter the effectiveness or toxicity of certain drugs.
Cancer Immunotherapies: Tapping into Innate Immunity

Most available immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapies, focus on immune cells called cytotoxic T cells, which are part of the adaptive, or specific, immune system. Cytotoxic T cells recognize and kill cancer cells that display specific molecules (antigens) on their surfaces.

Cancer researchers have turned to the innate, or nonspecific, immune system, as well, seeking to tap its potential for cancer immunotherapy. The innate immune system provides the first line of defense against infections and abnormal cells. This defense does not require the recognition of antigens. However, once an innate immune response has been initiated, an adaptive immune response is stimulated, and both work together to eliminate infections or other threats to the body.

The innate immune system provides the first line of defense against infections and abnormal cells.

NCI-funded investigators have recently found new ways to leverage the innate immune system against cancer and manipulate it to improve cancer immunotherapy. For example:

Harnessing Dendritic Cells to Activate T-cell Immunity

A group of NCI-funded researchers at the University of Pennsylvania has found a way to exploit dendritic cells, innate immune cells that process antigens and present them to T cells. Dendritic cells often express a protein called CD40, which triggers a cascade of biochemical reactions that prime T cells to attack tumor cells. In a mouse model of pancreatic cancer, activating CD40 in dendritic cells altered the microenvironment of the tumor, caused an expansion of T cells within it, and led to tumor destruction. Based on this work, clinical trials are underway in patients with pancreatic cancer, a difficult-to-treat disease that has thus far been resistant to immunotherapy approaches.

Helping Macrophages Engulf Cancer Cells

Macrophages are innate immune cells that engulf and digest cancer cells, cell debris, bacteria, and other foreign substances. Normal cells are protected from being eaten by macrophages because they display a protein called CD47 on their surface. In effect, CD47 is a “don’t eat me” signal to macrophages. Many cancer cells, however, also display CD47 on their surface, protecting them from macrophages. NCI-funded researchers at Stanford University and their collaborators have developed an antibody, now being tested in clinical trials, that blocks CD47, making cancer cells susceptible to attack and engulfment by macrophages. Read how Allen from Maryland benefited from this experimental drug on page 25. In addition, another group of University of Pennsylvania researchers recently demonstrated that the metabolism of macrophages can be “rewired,” enabling them to eat cancer cells even if they express CD47.

Engineering Natural Killer Cells to Target Cancer

Natural killer (NK) cells are yet another type of innate immune cell that recently have been used to treat cancer. For example, researchers are engineering CAR NK cells to improve their ability to kill cancer cells. Using NK cells overcomes a limitation of CAR T-cell therapy: the fact that personalized CAR T cells have to be made from the patient’s own cells. CAR NK cells can be made from another person’s blood cells and, so far, seem to cause fewer side effects than CAR T cells. A trial testing CAR NK cells in patients with B-cell lymphoma has just begun at the University of Texas MD Anderson Cancer Center.

Microbes: An Army of Helpers?

In the past several years, research on the microbiome has grown exponentially. Scientists have found that the microbiome is essential in shaping the development of innate and adaptive immunity and, in turn, the immune system shapes the microbiome.

Now, NCI-funded researchers are working to gain a better understanding of how the microbiome influences cancer development and the response to therapy. Recent findings show the promise of this emerging area of research:
Removing Microbes that Suppress Immunity in Liver Cancer

Metabolites produced by gut microbes appear to play an important role in antitumor immunity. For instance, a recent study conducted by scientists in NCI’s intramural research program showed that, in mice, the modification of bile acids by a particular type of gut bacteria species (Clostridium) can suppress innate immune cells called natural killer T (NKT) cells and inhibit their ability to control the growth of liver tumors. When the investigators used antibiotics to selectively kill the bacteria, NKT cells accumulated in the liver and inhibited liver tumor growth. Based on this laboratory research, a clinical trial initiated at the NIH Clinical Center is testing a combination of the antibiotic vancomycin, which kills Clostridium species, with other drugs that enhance antitumor immune responses.

NCI-funded researchers are working to gain a better understanding of how the microbiome influences cancer development and the response to therapy.

Identifying Microbes that Enhance (or Suppress) the Response to Cancer Therapy

NCI-funded researchers have revealed associations between the gut microbiome and responses to cancer immunotherapy. For example, investigators at MD Anderson and the University of Chicago have found that certain types of gut bacteria in patients with cancer are associated with clinical responses to immune checkpoint inhibitors. Research is shedding light on how these microbes might exert their effects, including by influencing the function of dendritic cells and their ability to initiate an attack by the adaptive immune system.

Disrupting Microbes to Prevent and Treat Colon Cancer

Researchers have also discovered that certain microbes are associated with the development of cancer. For instance, the bacterium Fusobacterium nucleatum is strongly associated with colorectal cancer. NCI-funded research indicates that this bacterial species affects the activity of both innate and adaptive immune cells, leading to the development of an immunosuppressive tumor microenvironment and promoting colorectal cancer progression. Scientists are using this knowledge to develop cancer prevention and treatment strategies aimed at disrupting the effects of this bacterium.

The Path to New Therapies: First, Answer Fundamental Questions

NCI-funded research on innate immunity and the interactions between resident microbial species and the immune system is revealing many new opportunities for additional progress against cancer. Achieving a better understanding of how bacteria interact with immune cells in patients with cancer will lead to entirely new therapeutic approaches, as well as improvements in existing treatments. In the future, it may even be possible to develop “bugs as drugs,” using genetically engineered microbes to promote potent antitumor immune responses.

It may even be possible to develop “bugs as drugs,” using genetically engineered microbes to promote potent antitumor immune responses.

To build on the progress that has been made, additional research is necessary to answer many fundamental questions: What bacterial species positively or negatively influence antitumor immune responses? What are the mechanisms by which bacteria exert their effects on the immune system in the context of cancer? How does altered composition of the bacterial species found in the gut influence susceptibility to cancer? What is the role of diet in these processes? Can other components of the innate immune system be harnessed for cancer therapy?

In addition, new resources, including better cancer models, are needed to support additional
basic research and preclinical drug development. Technologies that enable analyses of single tumor and immune cells and advanced tumor imaging will drive progress in this emerging area of research. In addition, ongoing collaborative efforts such as the Human Tumor Atlas Network will provide researchers with dynamic, detailed information about tumors and the components of their microenvironments.

Researchers have only scratched the surface in understanding the complexity of the immune system and microbiomes in the context of cancer. With continued investment in these areas, scientists will discover new strategies to prevent cancer and improve the lives of people who develop it.

**Researchers have only scratched the surface in understanding the complexity of the immune system and microbiomes in the context of cancer.**
Mark—Maryland

Senior Investigator, National Cancer Institute
Opportunities in Cancer Research: Artificial Intelligence

Artificial intelligence (AI) is everywhere: personal digital assistants answer our questions, robo-advisors trade stocks for us, and driverless cars will someday take us where we want to go. AI has penetrated our lives, and its use is exploding in biomedical research and health care—including across all dimensions of cancer research, where the potential applications for AI are vast.

AI excels at recognizing patterns in large volumes of data, extracting relationships between complex features in the data, and identifying characteristics in data (including images) that cannot be perceived by the human brain. It has already produced results in radiology, where clinicians use computers to process images rapidly, thus allowing radiologists to focus their time on aspects for which their technical judgment is critical. For example, last year, the Food and Drug Administration approved the first AI-based software to process images rapidly and assist radiologists in detecting breast cancer in screening mammograms.

Integration of AI technology in cancer care could improve the accuracy and speed of diagnosis, aid clinical decision-making, and lead to better health outcomes. AI-guided clinical care has the potential to play an important role in reducing health disparities, particularly in low-resource settings. NCI will invest in supporting research, developing infrastructure, and training the workforce to help achieve these goals and more.

Analyzing a Picture to Prevent Cervical Cancer

Mark Schiffman, M.D., M.P.H., has always had a passion for social justice. It led him to become a public health doctor with the intent of helping people. “I hope things I’ve done are helping people I’ll never meet,” he says.

Mark found a challenge—and an opportunity to realize that hope—in the study of why human papillomavirus (HPV) is such a strong carcinogen. HPV infection causes cervical cancer, the fourth most common cancer among women globally.

Recently, Mark and a team of researchers developed an artificial intelligence (AI) approach to analyze images for cervical precancer. They tested the approach using more than 60,000 cervical images from an NCI cervical cancer screening trial. The trial started 25 years ago in an area of Costa Rica that has high rates of cervical cancer. The investigators systematically collected cervical images from women who volunteered to participate and continued to observe them for up to 18 years to learn about the course of cancer development.

The AI algorithm was able to positively identify precancerous changes that required medical attention to prevent cancer. “The computer algorithm was at least twice as accurate as the best doctors we showed the images to,” Mark recalls. “By identifying cervical abnormalities that would likely progress, it was predicting 6 to 7 years into the future who would develop a precancer and who wouldn’t.”

Mark is especially heartened that this AI technology can be used easily in low- and middle-resource settings in the United States and elsewhere. “This has the potential to improve the lives of many women worldwide,” he affirms.
Artificial Intelligence (AI) is a computer performing tasks commonly associated with human intelligence. Humans are coding or programing a computer to act, reason, and learn. An algorithm or model is the code that tells the computer how to act, reason, and learn.

Machine Learning (ML) is a type of AI that is not explicitly programmed to perform a specific task but rather can learn iteratively to make predictions or decisions. The more data an ML model is exposed to, the better it performs over time.

Deep Learning (DL) is a subset of ML that uses artificial neural networks modeled after how the human brain processes information to learn from huge amounts of data. A well-designed and well-trained DL model is able to perform classification tasks and make predictions with high accuracy, sometimes exceeding human expert-level performance.

Integration of AI technology in cancer care could improve accuracy and speed of diagnosis, aid clinical decision-making, and lead to better health outcomes.

Emerging AI Applications in Oncology

NCI-funded research has already led to several opportunities for the use of AI. Here are some examples:

Improving Cancer Screening and Diagnosis

Scientists in NCI’s intramural research program are leveraging the capabilities of AI to improve cancer screening in cervical and prostate cancer. NCI investigators developed a deep learning approach for the automated detection of precancerous cervical lesions from digital images. Read more about this in Mark’s story on page 33.

Another group of NCI intramural investigators and their collaborators trained a computer algorithm to analyze MRI images of the prostate. Historically, standard biopsies of the prostate did not always produce the most accurate information. Starting 15 years ago, clinicians at NCI began performing biopsies guided by findings from MRI, enabling them to focus on regions of the prostate most likely to be cancerous. MRI-guided biopsy improved diagnosis and treatment when utilized by prostate cancer experts, but the method did not transfer well to clinics without prostate cancer expertise. The NCI clinicians used AI to capture their diagnostic expertise and made the algorithm accessible to clinics across the country as a tool to help with diagnosis and clinical decision-making.

The full potential of the MRI-guided biopsy developed by NCI researchers is being realized in clinics without prostate cancer-specific expertise because of this AI tool. New AI algorithms under development now aim to surpass the capabilities of well-trained radiologists by enabling the prediction of patient outcomes from MRI.

Aiding the Genomic Characterization of Tumors

AI methods can also be used to identify specific gene mutations from tumor pathology images instead of using traditional genomic sequencing. For instance, NCI-funded researchers at New York University used deep learning (DL) to analyze pathology images of lung tumors obtained from The Cancer Genome Atlas. Not only could the DL method accurately distinguish between two of the most common lung cancer subtypes, adenocarcinoma and squamous cell carcinoma, it could predict commonly mutated genes from the images.

In the context of brain tumors, identifying mutations using noninvasive techniques is a particularly challenging problem. With NCI support, an international team, including investigators at Harvard University and the University of Pennsylvania, recently developed a DL method to identify $IDH$ mutations noninvasively from MRI images of gliomas. These research findings suggest that, in the future, AI could help identify gene mutations in innovative ways.

Accelerating Drug Discovery

NCI is leveraging the power of AI in multiple ways to discover new treatments for cancer. The Cancer Moonshot℠ is supporting two major efforts...
Leveraging AI to Improve Detection of Cervical Precancer

Scientists in NCI’s intramural research program helped to develop an artificial intelligence (AI) approach using deep learning for the automated detection of precancerous lesions using cervical images. The goal was to develop a more-accurate and cost-effective screening method that could be used easily in low- and middle-resource settings. They tested the approach on more than 60,000 cervical images from an NCI study started 25 years ago in Costa Rica.

Cervical Cancer Screening Methods

The project compared multiple cervical screening methods, used at the beginning of the study in women who were followed for 7 years, including:

**Visual Appearance:** Photographs were taken after each study participant’s cervix had been rinsed with vinegar. Vinegar highlights changes to normal tissue caused by HPV infection, including precancer or cancer, by turning the tissue white. A gynecologist evaluated the pictures to identify precancerous or cancerous lesions. The sensitivity (identification of true positives) of this approach was 69%.

**Pap Smear:** Cervical cells were collected, affixed to a slide, and analyzed by a pathologist for the presence of precancerous or cancerous cells. The sensitivity of this approach was 71%.

**Automated Visual Evaluation:** A deep-learning, artificial intelligence approach was used to evaluate digitized images of the cervix in an automated process that predicted the probability that the image represented a case of precancer or cancer. The sensitivity of this approach was 91%.

The AI-Based Approach Was More Sensitive than Other Methods

The proportion of precancers or cancers that developed over the subsequent 7 years that were correctly identified at baseline (the beginning of the study) by each method:

in partnership with the Department of Energy (DOE) to leverage its supercomputing expertise and power for cancer research. In one effort, AI is being used to detect and interpret features of target molecules (e.g., proteins or nucleic acids that are important in cancer growth), make predictions for new drugs to target those molecules, and help evaluate the effectiveness of those drugs. Research is also being done to identify novel approaches for creating new drugs more effectively.

A project that is part of the second effort is using computational methods to model the interaction of KRAS protein with the cell membrane in detailed ways that were not previously possible. A cross-agency research team collaborating with the RAS Initiative developed a model of KRAS–lipid membrane binding to simulate the behavior of KRAS at the membrane. This model could help identify novel ways to inhibit the activity of mutant KRAS protein. This work will help scientists find new avenues to target mutations in the KRAS gene, one of the most frequently mutated oncogenes in tumors. In the future, this could be applied to other important oncogenes.

Improving Cancer Surveillance

The NCI–DOE collaboration is also enabling the application of DL to analyze patient information and cancer statistics collected by the NCI Surveillance, Epidemiology, and End Results (SEER) program. As part of this effort, DL algorithms were developed to extract tumor features automatically from pathology reports, saving thousands of hours of manual processing time. The goal of the project is to transform cancer care by applying AI capabilities to population-based cancer data in real time. This will help us better understand how new diagnostic methods, treatments, and other factors affect patient outcomes. Real-time data analysis will also allow for newly diagnosed individuals to be linked with clinical trials that may benefit them. NCI’s long-term investment in the SEER program and its infrastructure, coupled with newer investments in AI, will enable pattern recognition in population data that was impossible before. AI will aid in predicting treatment response, likelihood of recurrence (local or metastatic), and survival.

Applying AI capabilities to population-based cancer data in real time will help us better understand how new diagnostic methods, treatments, and other factors affect patient outcomes.

Realizing the Promise of AI in Oncology—and Avoiding the Pitfalls

The potential applications of AI in medicine and cancer research hold great promise. Leveraging these opportunities will require increasing investments and addressing some challenges that will have to be overcome.

Building an AI Cancer Research Community

The data science and AI communities will be important partners in realizing the promise of AI in cancer research. NCI can engage these communities by providing appropriate funding opportunities and access to data sources; linking cancer researchers and AI researchers; and supporting the training and development of a workforce with expertise in AI, data science, and cancer. Building on the NCI–DOE collaboration, a series of workshops are being held to build a community engaged in pushing the limits of current computational practices in cancer research to develop new computational technologies.

Bridging the Gap from Research to Practice

Currently, the use of AI in cancer research and care is in its infancy. Most research is focused on methods development, rather than on implementing those methods in clinical practice. NCI has an opportunity to lead the way in implementing AI in cancer care by supporting research to find effective pathways for clinical integration (including ways to understand uncertainty and validate AI approaches), educating medical personnel about the strengths and weaknesses of the technology, and rigorously assessing its benefits in terms of clinical outcomes, patient experience, and costs.
**Accessing Quality Cancer Data**

The lack of large, publicly available, well-annotated cancer datasets has been a significant barrier for AI research and algorithm development. The lack of benchmarking datasets in cancer research hampers reproducibility and validation. Support for annotation, harmonization, and sharing of standardized cancer datasets to drive AI innovation and support training and validation of AI models will be essential. With even greater volumes of data anticipated in the future, support for developing approaches to generate and aggregate new research and clinical data coherently will be critical for long-term success.

To support this work and to make cancer data broadly available for all types of research, NCI is refining policies and practices to enhance and improve data sharing. As part of those efforts, NCI is building a Cancer Research Data Commons (CRDC). One node of the CRDC is an Imaging Data Commons that will connect to The Cancer Imaging Archive, a unique resource of publicly available, archival cancer images with supporting data to enable discovery. NCI also recently launched the Childhood Cancer Data Initiative to accelerate progress for children, adolescents, and young adults with cancer by optimizing the collection, aggregation, and utility of research and clinical data.

NCI’s data aggregation and sharing efforts are crucial to moving AI and many areas of cancer research forward. As new sources of biomedical and health data emerge, the amount of information will continue growing faster than it can be interrogated. AI will be an essential tool for processing, aggregating, and analyzing the vast amounts of information the data hold to drive discovery and improve patient care.

**Understanding the Method Behind the Machine**

One challenge of AI, and DL specifically, is the “black box” problem: not fully understanding what features of the data a computer has used in its decision-making process. For example, a DL algorithm that predicts the optimal treatment for a patient does not provide the reasoning it used to make that prediction. Additional efforts are needed to reveal how algorithms arrive at a decision or prediction so that the process becomes transparent to scientists and clinicians. Making these algorithms transparent could help researchers identify new biological features relevant to disease diagnosis or treatment.

**NCI’s data aggregation and sharing efforts are crucial to moving AI and many areas of cancer research forward.**

Incorporating information about biological processes into the algorithm is likely to improve its accuracy and decrease dependence on large amounts of annotated data, which may not be available. One danger of the “black box” problem is that DL may inadvertently perpetuate existing unconscious biases. Researchers need to carefully consider how potential biases affect the data being used to develop a model, adopt practices to address and monitor those biases, and monitor performance and applicability of AI models.

With increased investments, NCI’s efforts to realize AI’s potential will lead to more accurate and rapid diagnoses, improved clinical decision-making, and, ultimately, better health outcomes for patients with cancer and those at risk.
Ross—Missouri

Steven H. and Susan U. Lipstein Distinguished Professor, Washington University in St. Louis
Opportunities in Cancer Research: Implementation Science

The enormous gap between what we know can optimize health and what gets implemented in everyday practice is a critical impediment to improving the health of cancer patients and survivors. Implementation science, a growing research field, uses a scientific approach to find the best ways to integrate proven, effective interventions into routine health care.

The field of implementation science bridges the divide between research and practice to improve patient and population health outcomes. It enables maximum impact for NCI’s investments in cancer research, with a focus on equity, so that even the most disadvantaged and underserved communities gain the benefits of the latest scientific advances.

Reducing Cancer Risk by Implementing Our Discoveries

For more than 30 years, Ross Brownson, Ph.D., has been a trailblazer in implementation science and cancer research. His passion is finding ways to help people be more active and receive access to cancer prevention and control interventions, particularly people from underserved populations.

Ross currently leads an NCI-funded study that will help state agencies deliver the most effective public health practices to meet the needs of their communities. The study team is collecting feedback, from hundreds of public health practitioners representing all 50 states, on what types of cancer prevention and control programs they provide to the public. He reasons that better understanding how to continue using evidence-based cancer prevention and control interventions and how to decrease the use of ineffective programs will benefit people across the country.

This work draws on Ross’s background as a former official with the Missouri Public Health Department, where he worked with local and state organizations in the 1990s to implement dozens of evidence-based physical activity programs in rural Missouri.

Leveraging his experience in implementing interventions in real-world settings, Ross returned to academia to better understand how to increase the use of evidence-based interventions in public health practice to improve population health. “Translating research more quickly into interventions, which is what implementation science is all about, can make a big difference in all of our lives,” he says.

“NCI has supported my research for many years,” Ross says appreciatively. “I’m now trying to open doors for the next generation of cancer implementation scientists.” His hope is that they will blaze new trails of their own.
NCI supports implementation science through a multifaceted approach: developing research initiatives, providing tools and resources to cancer researchers, disseminating knowledge on evidence-based cancer control interventions, and training investigators.

The Cancer Moonshot℠ Blue Ribbon Panel recognized important opportunities in implementation science and identified several specific areas for focused support:

- Accelerating the delivery of colorectal cancer screening, follow-up, and referrals to care in regions of the United States where screening rates are below national standards
- Enhancing the delivery of tobacco cessation treatments
- Developing approaches to identify and care for individuals with inherited cancer syndromes

The goal of NCI’s efforts is to ensure that health care practitioners and public health systems deliver evidence-based cancer care to patients and families that will improve outcomes for all populations. Effective implementation of evidence-based care in diverse settings, including low-resource environments, will help reduce the cancer disparities that exist today.

**Meeting Patients and Providers Where They Are**

For the last two decades, NCI has supported research to develop implementation strategies for interventions that improve cancer outcomes in health care and community settings. In addition, the NCI Community Oncology Research Program (NCORP) serves as a laboratory for conducting implementation science studies in cancer care delivery research. NCI-funded implementation science research has addressed post-treatment survivorship care, the use of cancer screening tests, and more. Examples of NCI-funded research projects include the following:

**Increasing Cancer Screening in Underserved Communities**

In Chicago’s Chinatown, Chinese immigrant women face language, cultural, and access barriers in obtaining breast and cervical cancer screenings and follow-up care. Because of these barriers, the screening rates for this population are only half of those of white women, resulting in poorer outcomes among this population. To address this issue, NCI funded a research partnership between Northwestern University, Rush University Medical Center, Mercy Hospital & Medical Center, and the Chinese American Service League to adapt and implement a community-based patient navigation program for breast and cervical cancer screening. Existing patient navigation services were adapted to be culturally relevant and were aligned with community structure, clinic processes, and policy contexts. From 2014 to 2017, navigation services were provided to 678 women. Although evaluation of this program is ongoing, it illustrates a promising approach for adapting patient navigation programs to underserved populations.

**Improving the Care of Cancer Survivors**

Much of the complex post-treatment care for survivors, who number 16.9 million and counting in the United States, has become the responsibility of primary care physicians, many of whom do not have the means, knowledge, or skills to provide comprehensive survivorship care. This care includes surveillance for disease recurrence (or new primary cancers) and interventions to mitigate the late and long-term adverse effects of cancer and its treatment.

To study the capacity for and barriers to the delivery of comprehensive survivorship services in primary care settings, NCI-funded researchers at Rutgers University evaluated the survivorship care provided by a diverse group of family medicine and internal medicine practices in multiple states. Their research revealed that major barriers to integrating comprehensive survivorship services into routine primary care included the lack of a recognized clinical category for cancer survivorship (i.e., describing a distinct patient population with unique needs), limited information or guidance from oncologists to inform actionable care plans, and inadequate information systems to support survivorship care.

These findings point to the need for evidence-based implementation strategies to improve the care of cancer survivors, a priority NCI continues to pursue, including through a recent request for applications aligned with the Childhood Cancer
## Implementation Science

Research discoveries have led to interventions, tools, and programs to better prevent, diagnose, and treat cancer. Yet these innovations can be underused and overused. Implementation science is a research endeavor that studies ways to optimally deliver these innovations to those who will benefit.

### What Are the Innovations?

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Tools</th>
<th>Programs</th>
</tr>
</thead>
</table>

### What Are the Implementation Challenges?

<table>
<thead>
<tr>
<th>Underuse</th>
<th>Overuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failing to deliver the innovation to those who would benefit</td>
<td>Delivering the innovation to those who will not benefit</td>
</tr>
</tbody>
</table>

### Who/What Is Affected?

<table>
<thead>
<tr>
<th>Policy</th>
<th>Community</th>
<th>Health Care System</th>
<th>Provider</th>
<th>Individual</th>
</tr>
</thead>
</table>

### How Do We Improve Implementation?

<table>
<thead>
<tr>
<th>Interactive Assistance</th>
<th>Adapt and Tailor</th>
<th>Support Practitioners</th>
<th>Engage Consumers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working with stakeholders during implementation</td>
<td>Modifying implementation based on needs</td>
<td>Empowering them to effectively implement the innovations</td>
<td>Involving individuals and families directly</td>
</tr>
</tbody>
</table>

### How Do We Know If Implementation Is Successful?

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Uptake</th>
<th>Cost</th>
<th>Fidelity</th>
<th>Sustainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovation is perceived to be appropriate to stakeholders</td>
<td>Innovation is used</td>
<td>Acceptable cost of supporting innovation delivery</td>
<td>Innovation is delivered as intended</td>
<td>Innovation is effectively delivered over time</td>
</tr>
</tbody>
</table>

### What Are the Desired Outcomes?

<table>
<thead>
<tr>
<th>Increased Years of Life</th>
<th>Improved Quality of Life</th>
<th>Health Equity</th>
</tr>
</thead>
</table>
Survivorship, Treatment, Access, and Research (STAR) Act. Included in this funding opportunity are implementation studies to develop and evaluate interventions to improve survivorship for these populations.

Promoting Wellness in Low-Wage Worksites

Small businesses (workplaces with fewer than 200 employees) in low-wage industries (e.g., food services, entertainment and recreation, retail trade) are often unable to implement health promotion interventions. NCI-funded researchers at the University of Washington evaluated the effectiveness of HealthLinks, a program developed in partnership with the American Cancer Society to support healthy eating, physical activity, tobacco cessation, and breast, cervical, and colon cancer screening for employees of small businesses in low-wage industries in Washington State.

The researchers measured employers’ commitment to change, as it is usually assumed that this commitment is a prerequisite for implementing and sustaining a systemic change. However, the researchers showed that planning and technical support, more than commitment or motivation, were the keys to effective implementation. Thus, implementation strategies can improve the delivery of care even when leadership lacks commitment.

Setting the Foundation

To build the field of implementation science in oncology, NCI provides resources, training, and collaborative opportunities. For example, the institute is:

Building the Implementation Science Knowledge Base

NCI created databases that provide researchers and practitioners access to resources that can help with the design, implementation, and evaluation of evidence-based cancer control programs. Since 2003, NCI has reviewed and posted more than 200 peer-reviewed cancer control intervention and program materials on the Research-Tested Intervention Programs (RTIPs) website. The website requires program developers to include materials needed for their programs to be implemented in a range of community and health care settings and rates the programs on the strength of evidence and readiness for implementation.

Strengthening the Implementation Science Workforce

NCI is investing in education and training programs to develop a workforce of implementation researchers to move the field forward. As one example, in 2018, NCI began hosting an annual training institute, the Training Institute for Dissemination and Implementation Research in Cancer (TIDIRC), that has provided more than 100 researchers with a thorough grounding in implementation science across the cancer control spectrum. NCI also supports an additional training program with the National Institutes of Health and Department of Veterans Affairs to build the workforce throughout the health research community. Nearly 350 investigators have participated in this training since 2011.

NCI is investing in education and training to develop a workforce of implementation researchers to move the field forward.

The Future: Precision Implementation

The field of implementation science holds promise for reducing the burden of cancer and improving the health of all Americans. Priority areas for NCI include improving health equity and access to evidence-based cancer care, ensuring sustainability of evidence-based practices, and discontinuing ineffective or harmful practices. Read more about this area of research in Ross’s story on page 39.
control interventions. Each center will establish implementation laboratories from existing clinical and community sites that will facilitate implementation in real-world settings.

In the long term, NCI aims to support a rapid-learning health care system by building and disseminating the implementation science knowledge base. A rapid-learning health care system harnesses ongoing data collected on patients, providers, and systems to drive real-time, continuous improvements in the delivery of care.

**NCI aims to support a rapid-learning health care system by building and disseminating the implementation science knowledge base.**

Pooling information across thousands of clinical and community practices, where interventions are adopted and sustained, will teach stakeholders how to develop effective implementation strategies in varied settings. A data ecosystem for implementation science will enable researchers and other stakeholders to identify successes, limitations, and targeted goals for future implementation science projects.

NCI’s investments in this area of research will move us toward a future of “precision implementation,” where interventions are adopted, accepted, and sustained at an optimal level within the range of contexts and populations in which they are used.
Jerome—Louisiana
Prostate Cancer Survivor
Strengthening the Cancer Research Enterprise

Scientific opportunities for researchers abound thanks to the great progress and strong foundations of basic science enabled by NCI’s support of the national cancer research system. NCI remains strongly committed to training investigators and taking advantage of the opportunities to establish or reinforce infrastructures that advance science. These remain pivotal components in our work to reduce the burden of cancer and improve the health of Americans.

NCI’s research enterprise helps train the next generation of cancer researchers, provides investigators with mechanisms that promote innovative thinking, coordinates the research and clinical trials infrastructure, and makes diverse resources available to the cancer research community. The basic and applied research conducted by NCI-supported scientists and organizations underpins advances in cancer prevention, detection, and treatment that produce better outcomes for patients, those at risk of cancer, and survivors.

Supporting the Cancer Research Workforce

To strengthen the cancer research enterprise, NCI develops and supports a cadre of exceptional scientists from a variety of disciplines across the career continuum—from students just starting to explore a career path to well-established cancer investigators. Having a community of researchers from diverse backgrounds and at all levels of expertise strengthens cancer research and its translation to patient care.

Treating Prostate Cancer Closer to Home

Jerome combines two passions, sports and cooking, when he makes gumbo for his buddies to enjoy as they watch their home team, the New Orleans Saints, play football. When he learned in 2018 that he had advanced prostate cancer, Jerome thought he might have to travel 350 miles for treatment at an NCI-Designated Cancer Center. He worried about missing work days, cooking on game days, and his friends.

However, he learned of an opportunity to join a phase 3 NCI-supported clinical trial offered locally through LSU Health New Orleans’s Stanley S. Scott Cancer Center, an NCI Community Oncology Research Program community site. The trial provides standard therapy for all enrollees, with two arms of the study also testing the efficacy of additional radiotherapy or surgery.

Jerome hesitated to enroll initially. Like many people with cancer, he had concerns about participating in an experimental study. After discussing his concerns with his doctor, Jerome decided to join the trial and was treated with hormone, radiation, chemotherapy, and, in early 2019, surgery to remove his prostate. A few months after a follow-up visit with his doctor, he was ecstatic to hear there was no evidence of disease remaining.

During treatment, Jerome has been traveling only 20 minutes from his house to his doctors. It was a big relief not having to take off work for an unknown time and go a long distance for treatment. “NCORP offered everything I needed,” he smiles, “here in my backyard.”
NCI Invests in Scientists at Every Career Stage

NCI supports 71 NCI-Designated Cancer Centers across the nation. These cancer centers are key...
partners in NCI's efforts to speed the process of discovery and bring the benefits of cancer research to the public. The cancer centers develop and translate scientific knowledge from promising laboratory discoveries into new treatments for patients with cancer.

Many of the cancer centers are located in communities with special needs and serve specific populations. Each year, approximately 250,000 patients receive their cancer diagnoses at an NCI-Designated Cancer Center, and thousands of patients are enrolled in clinical trials at these cancer centers. An even larger number of patients are treated at a cancer center each year, such as pediatric patient Rihanna on page 7.

**NCI Community Oncology Research Program (NCORP)**

To bring the latest scientific advances to community settings where the majority of patients with cancer are treated, NCI supports NCORP, a national network that conducts cancer prevention and treatment clinical trials as well as cancer care delivery research (CCDR).

In 2018, nearly 3,300 participants were accrued to CCDR studies at some of the 1,000 community sites, local hospitals, physician practices, and other organizations that participate in NCORP. In addition, NCORP is contributing significantly to enrolling patients in the NCI-MATCH trial. In partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, NCORP is helping to enroll 4,000 patients in the New-Onset Diabetes Cohort study, to study the link between new-onset diabetes and pancreatic cancer.

To address and reduce cancer disparities, NCORP has designated 12 Minority/Underserved Community Sites in areas with patient populations comprised of at least 30% racial/ethnic minorities or rural residents. Jerome’s experience (see page 45) highlights the value that NCORP brings to more diverse patient populations where they live and work.

**National Clinical Trials Network (NCTN)**

Cancer clinical trials allow researchers to evaluate new ways to prevent and detect cancer, improve therapies, and enhance the quality of life of patients during and after treatment. During fiscal year 2018, more than 30,000 new patients enrolled in NCI-sponsored or -supported clinical trials at locations across the United States and Canada through NCTN.

This network now includes more than 3,000 study sites that work to implement and complete clinical trials far more rapidly than in the past. NCTN’s structure includes one pediatric and four adult research groups, with 30 centers designated as lead academic research sites. Many investigators at other medical centers participate in NCTN trials, including researchers at NCORP sites and NCI-Designated Cancer Centers.

**Partnerships**

NCI partners with many federal and private-sector organizations to facilitate complex research programs that spur innovation, ensure the judicious use of public resources, and continue to help reduce the burden of cancer in the United States and beyond. A few of NCI’s many partnerships include:

- Collaboration with the Department of Veterans Affairs (VA) through the NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE) program, for example, is helping VA medical facilities in 11 states to enroll patients directly in NCI-supported clinical trials, making it easier for veterans to access state-of-the-art cancer treatments.

- The Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) network is a Cancer Moonshot℠ effort through which NCI and the VA work with the Department of Defense to provide personalized cancer care based on gene and protein expression in the tumors of individual patients.

- NCI is collaborating with the Department of Energy (DOE) on a Cancer Moonshot initiative called the Joint Design of Advanced Computing Solutions for Cancer, a program that applies cutting-edge computing technologies to: identify promising new treatment options, deepen our understanding of cancer biology, and improve our understanding of the impact of new diagnostics and treatments, as well as patient characteristics, at the national level.

- NCI, the Foundation for NIH, and 11 leading pharmaceutical companies are engaged in a public–private research collaboration...
called the Partnership for Accelerating Cancer Therapies (PACT) as part of the Cancer Moonshot with the aim of identifying, developing, and validating robust biomarkers (standardized biological markers of disease and treatment response) to advance new cancer immunotherapy treatments.

Resources

One of the ways NCI supports the national cancer research enterprise is by providing resources to individual investigators and institutions. NCI’s Resources for Researchers provides a directory of NCI-supported tools and services for cancer researchers. Most resources are free of cost and available to anyone.

In addition, through partnerships with industry, NCI provides rapid access to therapeutic agents for use in preclinical and clinical studies via the NCI Formulary. In 2018, investigators from more than 300 clinical research centers accessed the formulary, which, to date, contains 30 agents provided by 10 companies.

The Surveillance, Epidemiology, and End Results (SEER) Program is another well-used resource that provides essential information for tracking the nation’s progress against cancer and enables researchers to explore and explain trends in cancer incidence, mortality, and survivorship.

Strengthening Small Business Innovation and Commercialization

Through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs, NCI supports US-owned small businesses to develop and commercialize technologies to diagnose, treat, and prevent cancer. Successful commercialization of these innovations means that doctors and their patients can access cutting-edge cancer-related technologies to improve outcomes.

NCI’s SBIR/STTR Programs have supported the development of numerous technologies since 1982. In 2018, the portfolio contained 475 projects including drugs, in vitro diagnostics, devices, and other technologies.

For example, SBIR supported the development of CYAD-101, a CAR T-cell therapy made from healthy donor immune cells instead of a patient’s own immune cells. CYAD-101 is being tested as a treatment for metastatic colorectal cancer but has the potential to treat other cancers as well. Following the Food and Drug Administration’s (FDA) approval of an investigational new drug application for CYAD-101 in 2018, three phase 1 trials were designed to evaluate the efficacy and optimal dosage of this CAR T-cell therapy against several other cancers that have been challenging to treat, including bladder, pancreatic, ovarian, and triple-negative breast cancer.

A recent economic impact study showed that the SBIR/STTR Programs can improve the lives of patients by strengthening the role of small businesses that develop innovative cancer technologies. The study found that NCI received a strong return on investment in supporting small businesses, with an estimate as high as $33 returned for every $1 invested.

Conducting Research at NCI

While working to build scientific knowledge; advance cancer prevention, detection, and treatment; and improve the lives of patients and survivors, researchers in NCI’s intramural research program (IRP) have collaborated with more than 2,000 extramural investigators at more than 800 academic institutions across the United States, and from 68 countries around the world.

The IRP consists of two components: the Center for Cancer Research, which focuses on solving important, challenging, and neglected problems along the cancer continuum from fundamental research to patient care; and the Division of Cancer Epidemiology and Genetics, which works to uncover the causes of cancer and the means for preventing it through studies of risk factors, such as lifestyle choices, genetic predisposition, and environmental exposures.

IRP investigators, fellows, and visiting scientists from around the world conduct basic, clinical, and population-based research and are encouraged to explore the translation of relevant findings from the laboratory to the clinic. High-risk research and clinical trials that would be difficult for the extramural community to conduct or would not be a priority for industry are performed in NCI research laboratories, offices, and at the NIH.
NCI SBIR/STTR Program Garners a Strong Return on Investment

NCI INVESTMENT FROM 1998 THROUGH 2010:

$787 M
IN PHASE II AWARDS

690
PHASE II AWARDS

IMPACT AND OUTCOMES FROM 1998 THROUGH 2018:

$9.1 B
IN TOTAL SALES OF PRODUCTS AND SERVICES

247
COMMERCIALIZED PRODUCTS

$26.1 B
IN TOTAL US ECONOMIC OUTPUT

107,918
NEW US JOBS


Clinical Center. NCI investigators’ ability to work with patients from all over the world facilitates clinical research on rare cancers, which may benefit patients with these diseases and produce insights relevant to more common cancers.

The IRP can claim many accomplishments. In 2018, IRP investigators opened 40 new cancer trials and enrolled more than 4,000 patients in more than 250 clinical research studies. During 2017 and 2018, FDA approved three drugs that IRP scientists developed in concert with extramural partners, including avelumab (Bavencio) to treat Merkel cell cancer, axicabtagene ciloleucel (Yesclara) for B-cell lymphoma, and the immunotoxin moxetumomab pasudotox-tdfk (Lumoxiti) for hairy cell leukemia.

IRP scientists and extramural colleagues are also developing the therapy selumetinib to treat pediatric and adult patients who have a genetic syndrome called neurofibromatosis 1 (NFI); selumetinib received FDA’s orphan drug status in 2018. Other IRP researchers continue to study the epidemiology and carcinogenesis of human papillomavirus (HPV) infections and identify populations at risk of HPV-associated cancers.
To find answers to difficult problems currently facing the cancer research community, the IRP recently launched several programs that focus on liver cancer, rare tumors, and “RASopathies” (difficult-to-treat cancers driven by RAS mutations). Researchers are studying large cohorts to better identify populations at risk for cancer, including a major effort to evaluate factors influencing lung cancer risk among never smokers (Sherlock-lung) and common and rare genetic susceptibility for breast cancer (the Confluence Project). The IRP is bolstering the NCI Natural Products Repository, a national resource of natural chemical compounds for researchers developing cancer drugs.

**Frederick National Laboratory for Cancer Research (FNLCR)**

NCI sponsors FNLCR, a national laboratory dedicated to improving human health through discovery and innovation in biomedical research. FNLCR offers unique partnership opportunities for academia, government, and the private sector for rapidly addressing the most difficult challenges in cancer prevention, treatment, and control. The laboratory provides cancer researchers a bridge between basic research and clinical practice with support that is not readily available elsewhere.

Two examples of the types of projects spearheaded by FNLCR are:

- **RAS Initiative**: The family of oncogenes called RAS, when mutated, drive 30% of all human cancers, including 95% of pancreatic cancers and 45% of colorectal cancers. Research has shown that association with the cellular membrane is necessary to initiate KRAS protein signaling. RAS Initiative researchers recently reported new information about how KRAS interacts with the cell membrane and identified multiple factors that might be targeted to disrupt this interaction.

- **Cancer Distributed Learning Environment (CANDLE)**: NCI and FNLCR researchers collaborate with DOE and data scientists from four DOE national laboratories to develop new supercomputing capabilities for precision oncology. CANDLE is an open source software platform providing artificial intelligence methodologies to help accelerate cancer research. As part of this collaboration, data scientists and cancer researchers are working closely together to build the capability to use cancer data to develop predictive models for drug responses, provide better molecular understanding of cancer growth, and support decisions on individualized treatments.

**FNLCR offers unique partnership opportunities for academia, government, and the private sector for rapidly addressing the most difficult challenges in cancer prevention, treatment, and control.**