
NIH
NATIONAL CANCER INSTITUTE
Annual Plan
& Budget Proposal
for Fiscal Year 2019
U.S. Department of Health & Human Services | National Institutes of Health

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INVESTING IN THE FUTURE OF CANCER RESEARCH

Highlights of the *NCI Annual Plan & Budget Proposal for Fiscal Year 2019*

Every day, scientists and physicians dedicated to cancer research work to make discoveries that will advance new treatments and tools into the clinic. Patients participate in clinical trials with the hope of finding new options for themselves and producing better outcomes for future patients who will face the same disease. Their combined efforts—enabled by research funding—have led to new ways to prevent, detect, and treat cancer and a 25% decline in the rate of death from cancer over the past two decades.

Despite this progress, more work remains. Nearly 40% of Americans will be diagnosed with cancer in their lifetimes. In 2017, cancer is expected to take the lives of about 600,000 adults and 2,000 children in the United States. Many of us have had a family member, friend, or neighbor with cancer or have been affected by cancer ourselves. Continued progress requires strong and sustained federal investment in cancer research.

The National Cancer Institute (NCI) is the federal government's principal agency for cancer research and training. NCI leads, conducts, and supports cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives. As the largest funder of cancer research in the world, NCI supports investigators to advance a broad portfolio of research—from laboratory discoveries to clinical trials to population sciences. NCI encourages collaboration between scientists and organizations, conducts a rigorous and accountable funding process, and works with stakeholders to ensure that the national investment in cancer research has maximum impact.

There is strong national support for the work NCI funds. The Cancer Moonshot℠, which aims to accomplish a decade's worth of research in 5 years, is just one example of a targeted effort with specific resources for making dramatic advances against this disease.

NCI puts forward an annual plan and budget proposal that highlights the impact of the nation's investment in cancer research and directs attention to several areas for which additional support will enable more progress. The stories of investigators found in this document illustrate the innovative research catalyzed by NCI-support, and the stories of patients and cancer survivors highlight how NCI's investments in research help people live healthier lives.

Research Opportunities

Building on the momentum made in the past few decades requires support for all areas of cancer research, from basic science to cancer survivorship. NCI's commitment to train the next generation of cancer researchers is unwavering and cuts across all research areas. The *Annual Plan and Budget Proposal for Fiscal Year 2019* includes funds for exceptional opportunities in the following research areas.

UNDERSTANDING THE MECHANISMS OF CANCER

Cancer is a complex disease that requires an in-depth understanding of how genetic, behavioral, and environmental factors contribute to its development. Discoveries in basic scientific research on the growth, survival, and spread (metastasis) of cancer cells in the body have been, and continue to be, essential for continued progress. Part of NCI's mission is to support the basic scientific research that will lead to new ways to prevent, detect, and treat cancer, thereby enabling people to live longer, healthier lives. Two areas of research opportunity are understanding and therapeutically targeting the molecular drivers of cancer and understanding and finding new ways to control cancer metastasis.

PREVENTING CANCER

Improved cancer prevention means fewer people will face a diagnosis of cancer and the physical, financial, social, and psychological harms of the disease and its treatment. NCI-supported research informs efforts to minimize human exposure to cancer-causing agents in the environment and improve screening to detect and treat precancerous growths before they develop into cancer. An emerging area of opportunity is the development of vaccines to prevent not only the cancers that are caused by viruses but also cancers that are not caused by viruses.

DETECTING & DIAGNOSING CANCER

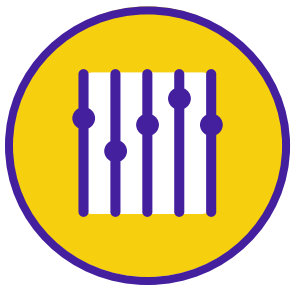
Early detection is a proven strategy for saving lives from cancer. NCI funds research to improve cancer detection in its early stages, when it may be most treatable, and to accurately assess how likely it is that a precancerous growth will progress to life-threatening disease. An area of opportunity includes developing new approaches, including liquid biopsies and other less-invasive methods, for the early detection of precancers and early cancers. These approaches have the potential to increase the number of cancers for which we have clinically effective screening programs as well as to improve the technologies currently used to screen for cancer.

TREATING CANCER

NCI's commitment to developing new treatments for cancer patients spans basic research to discover the mechanisms of cancer, preclinical research to investigate the anticancer effects of therapies that target these mechanisms, and clinical research to test new therapies in patients. Despite recent advances in targeted therapy and immunotherapy, more needs to be done to substantially improve the outlook for both adults and children with cancer. Three areas for further investment include developing combination therapies, biomarker-guided immunotherapies, and precision medicines that target specific abnormalities in a patient's cancer.

ADVANCING PUBLIC HEALTH IN CANCER

NCI supports research focused on improving the delivery of cancer care and designing interventions at the individual and population levels to improve cancer prevention, screening, treatment, and survivorship. Some areas of opportunity include understanding how body weight and physical activity influence cancer risk and outcomes; further reducing tobacco use; delivering high-quality cancer prevention, screening, and treatment to all regions of the country; and improving the quality of life of cancer survivors.



REDUCING CANCER DISPARITIES

Advances in cancer research do not benefit all people equally. Some cancer disparities can be attributed to differences in access to, utilization of, and quality of care, but biology and lifestyle factors are also important. The biology of cancer disparities requires more research and attention to improve the outcomes of patients and individuals at risk of cancer. Innovative ways to mitigate the effects of biology and lifestyle factors and to improve access to quality care are needed to ensure the best cancer outcomes for all Americans. This will require additional studies of cancer in underrepresented racial/ethnic populations and greater participation by members of these populations in clinical trials. Special attention to the cancer needs of rural populations is also essential.

LEADING THE NATION'S PROGRESS AGAINST CANCER

Groundbreaking research and training supported by the National Cancer Institute (NCI) has led to a substantial reduction in the burden of cancer in the United States. The development of improved screening and prevention methods, novel approaches for the diagnosis and detection of cancer, and innovative treatments have all contributed to this progress.

The National Cancer Institute

NCI is the federal government's principal agency for cancer research and training. It is part of the National Institutes of Health, which is one of 11 agencies that comprise the Department of Health and Human Services. NCI leads, conducts, and supports cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives.

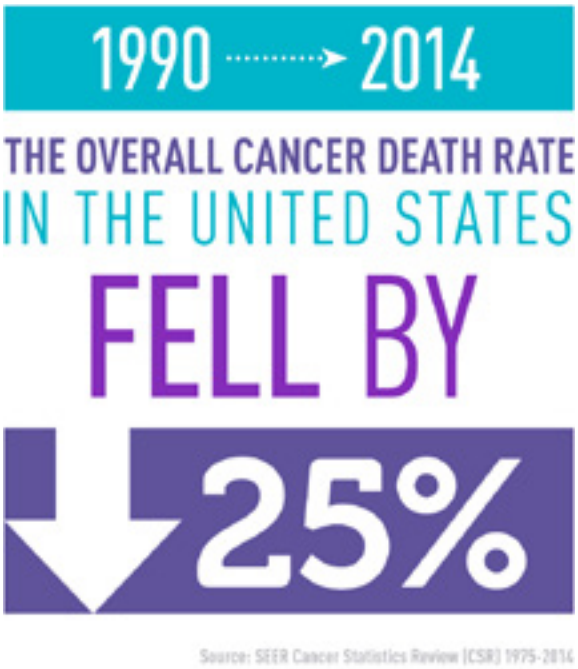
As the largest funder of cancer research in the world, NCI supports investigators working across the United States and in other countries. This support is advancing a broad portfolio of research—from basic laboratory science to clinical trials and population science—to improve our understanding of cancer and cancer prevention, diagnosis, treatment, and survivorship. NCI encourages collaboration between scientists and organizations, conducts a rigorous and accountable funding process, and works with stakeholders to ensure that the nation's investment in cancer research has maximum impact.

The *NCI Annual Plan and Budget Proposal*

The National Cancer Act of 1971 authorizes NCI to prepare an annual budget proposal directly for the President and Congress. This proposal represents NCI's best professional judgment about the funding needed to make the most rapid progress against cancer.

The *Annual Plan and Budget Proposal for Fiscal Year 2019* highlights the impact of the nation's continuing investment in cancer research and directs attention to several areas for which additional support will enable greater and faster progress. The stories of investigators who have devoted their careers to cancer research illustrate some of the innovations driven by NCI-supported science. The stories of patients and survivors highlight how NCI's investments in research can improve lives and reveal challenges that remain to be addressed.

As this plan shows, the research community—under NCI's leadership—is making pivotal advances against cancer. However, much more still needs to be done to increase our understanding of the many diseases we call cancer and extend the benefits of research to even more people.



The Return on Cancer Research Investment

Improvements in cancer prevention, screening, and treatment, fostered by dedicated researchers across the nation and patients who volunteer to participate in clinical trials, have helped to reduce the burden of cancer in the United States. The clearest sign of this progress is the steady decline in the rate of cancer deaths, which has continued for more than two decades. Specifically, the cancer death rate among adults declined by 25% from 1990 through 2014, and the death rate among children and adolescents (age 19 and younger) declined by 35%. Moreover, of the top 10 causes of death among Americans, only cancer showed a decrease from 2014 to 2015.

For most of the last half of the 20th century, the rate of cancer deaths rose sharply, driven largely by cigarette smoking. Beginning in the early 1990s, however, cancer death rates started to decline because of reductions in tobacco use, as well as increased utilization of other cancer prevention measures, better screening, and new treatments. Continued progress in these areas should ensure that the downward trend in the overall rate of cancer death is sustained or accelerated to prevent the loss of even more lives.

Another sign of progress is that the overall rate of cancer incidence for men and women combined declined steadily from 2007 through 2014. However, when the rates for men and women were analyzed separately, a decline was observed only for men; the incidence rate for women remained stable during this period. Nevertheless, these separate trends for men and women stand in sharp contrast with the rising rates of cancer incidence observed for both sexes before the beginning of the 21st century.

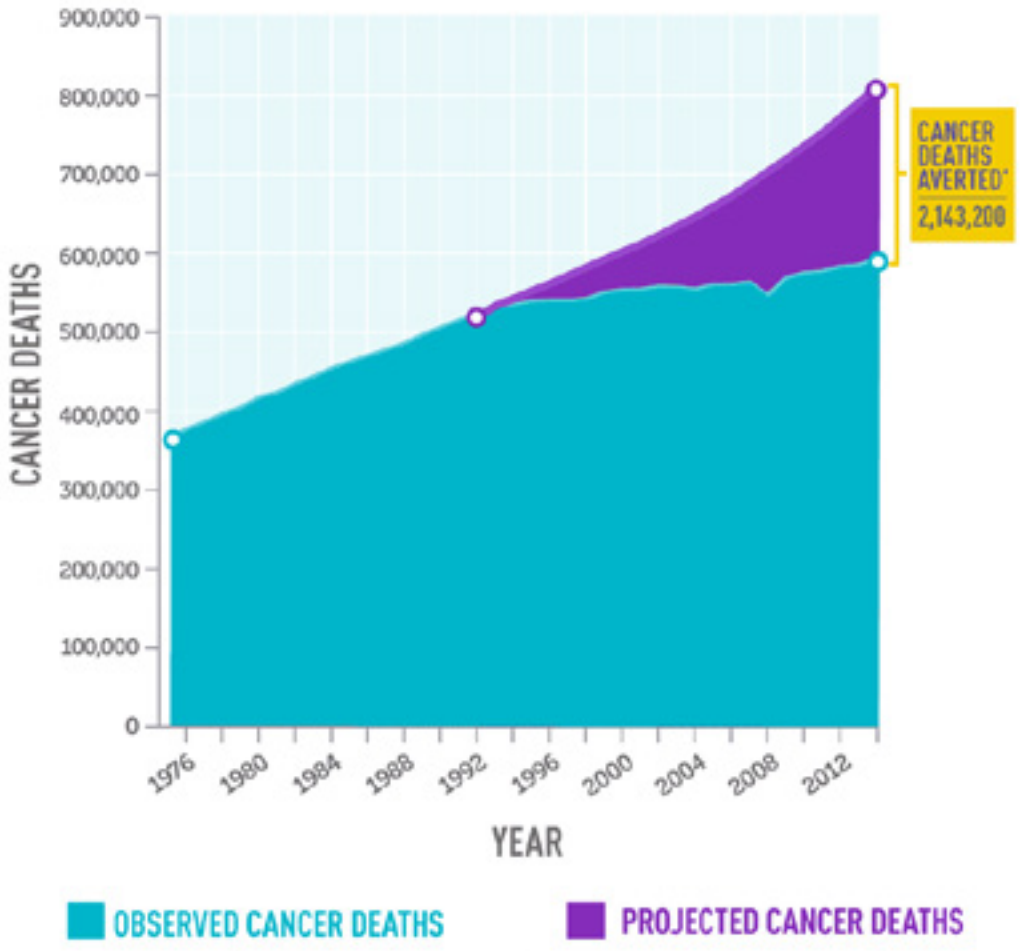
The Need for Greater Progress

The surest indicator of the need for greater progress is that an estimated 1.7 million new cases of cancer and 600,000 cancer deaths will occur among U.S. adults in 2017 and approximately 15,000 new cases of cancer and 2,000 cancer deaths will occur among U.S. children and adolescents. In addition, the incidence and mortality rates for some cancers, such as liver cancer, are still increasing, and the numbers of new cancer cases and cancer deaths will continue to grow as the population ages.

Cancer Disparities

Despite the overall decreases in U.S. cancer incidence and mortality, certain population groups in this country suffer disproportionatly from some cancers. Although many of the differences in cancer incidence and mortality between population groups can be attributed to access to cancer screening tests and quality cancer care, additional factors, including genetics and lifestyle factors, 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.

Cancer Deaths Averted in Men & Women from 1991 to 2014

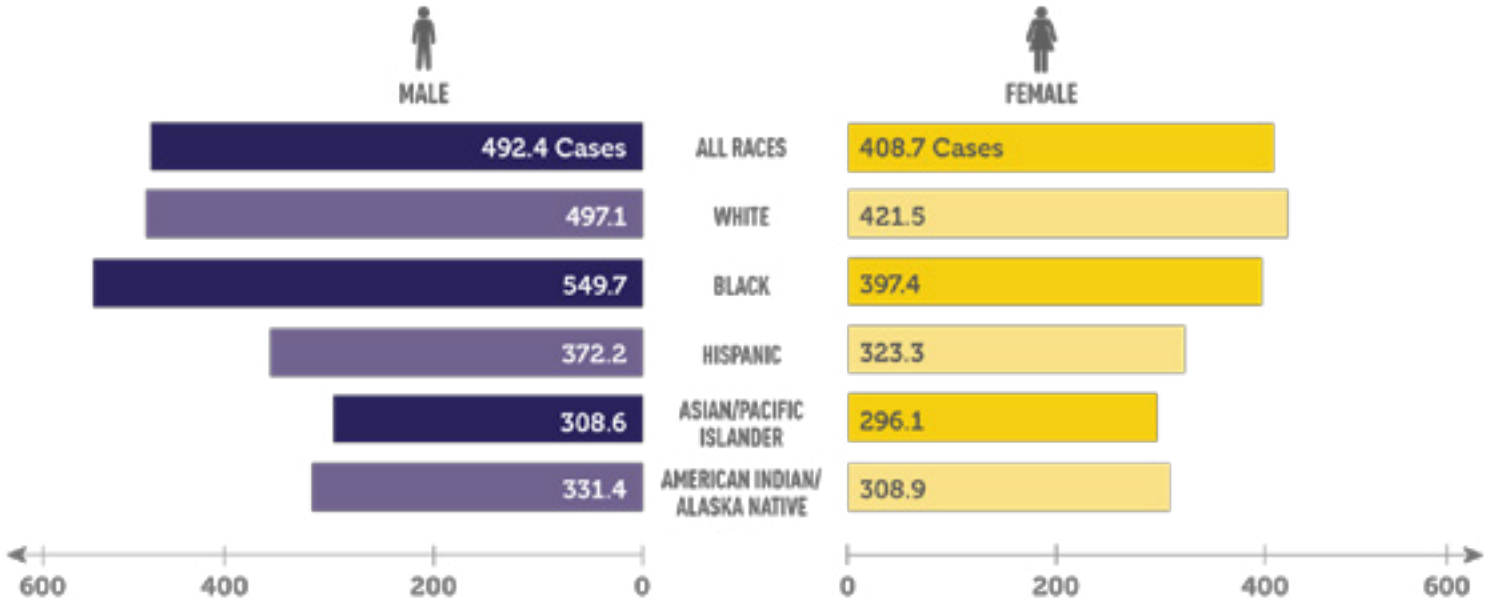


* Represents the difference between the number of observed cancer deaths and the number of projected cancer deaths that would have occurred had cancer death rates remained at their peak.

Adapted from: Siegel RL et al, Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30. John Wiley & Sons, Inc. © 2017 American Cancer Society

Number of New Cancer Cases Each Year

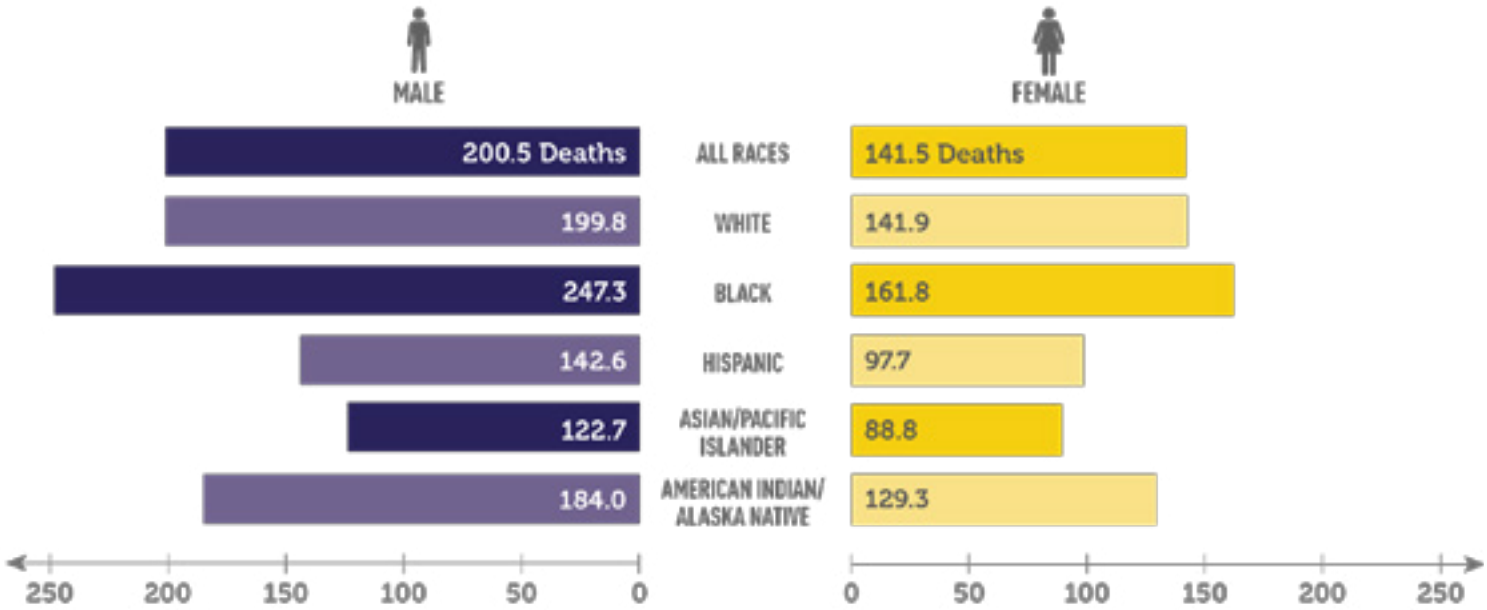
Per 100,000 Persons by Gender and Race/Ethnicity: All Cancers



Source: SEER 18, 2010-2014

Number of Deaths Each Year

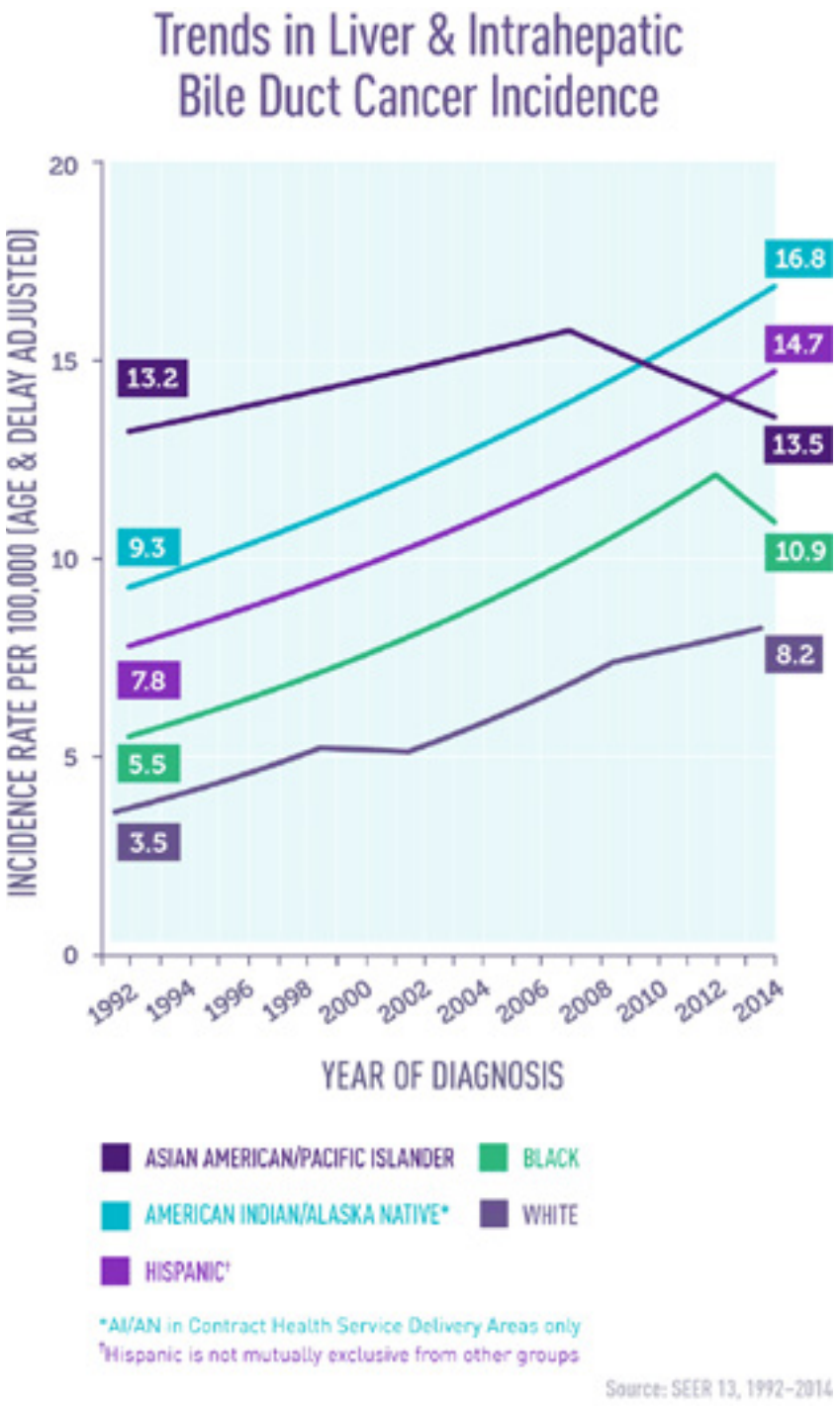
Per 100,000 Persons by Gender and Race/Ethnicity: All Cancers

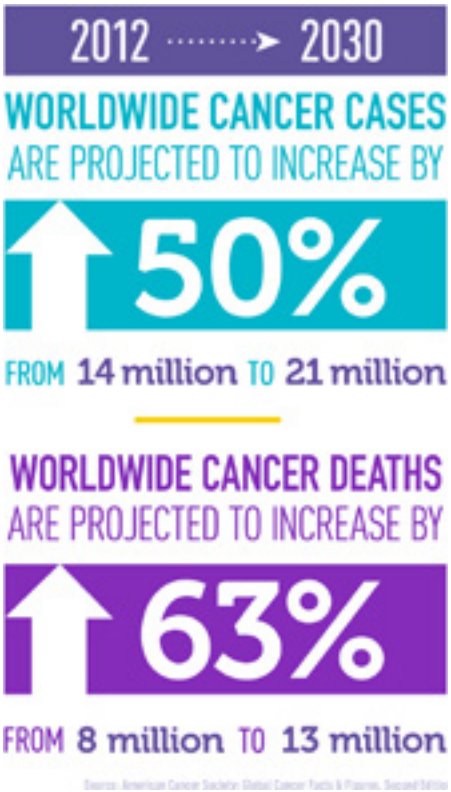


Source: SEER 18, 2010-2014

Liver cancer is one example for which disparities exist. The rates of incidence and death for this cancer are substantially higher among American Indians/Alaska Natives, Asian Americans/Pacific Islanders, Hispanics, and African Americans than among whites. The reasons for these disparities are not clear and represent an area of research opportunity.

One new NCI initiative focused on understanding biological factors that may contribute to cancer disparities is the Early Onset Malignancies Initiative (EOMI), which was announced in 2016. In this initiative, researchers are seeking to understand why certain racial and ethnic groups have increased risks of developing specific cancers at an early age. Samples of early-onset tumors from four different racial/ethnic populations will be collected for detailed molecular analyses, along with information about treatment(s) received, tumor response, and patient outcomes. Characterization at the molecular level will enable researchers to determine if genetic factors are contributing to disparities in early-onset cancer among the different population groups. Data from the study may enable researchers to answer questions about the molecular determinants of early-onset disease and possible associations with treatment response or prognosis.





Global Burden of Cancer

Worldwide, more than 21 million new cases of cancer are predicted to occur in 2030, an increase of 50% over the 14 million cases that occurred in 2012. It is also predicted that 13 million cancer-related deaths will occur in 2030, an increase of nearly 63% over the 8 million cancer-related deaths that occurred in 2012. Most of this growing burden of cancer incidence and mortality will be borne by low- and middle-income countries.

To address this growing global burden of cancer and to gain knowledge that can be applied in the United States as well, NCI facilitates global collaborations with other U.S. agencies, foreign governments, nongovernmental organizations, and companies to support clinical trials and medical device development for use in low-resource settings.

The Cancer Moonshot℠

In 2016, NCI was afforded a unique opportunity to advance cancer research through the Cancer Moonshot initiative. The goals of this initiative are to accelerate progress in cancer research, increase cooperation and collaboration among members of the cancer research community and other stakeholders within and outside the federal government, and expand data sharing.

Under the initiative, the research community identified 10 areas of research opportunity where progress could be accelerated with additional funding. NCI was given primary responsibility for scientific oversight of the initiative.

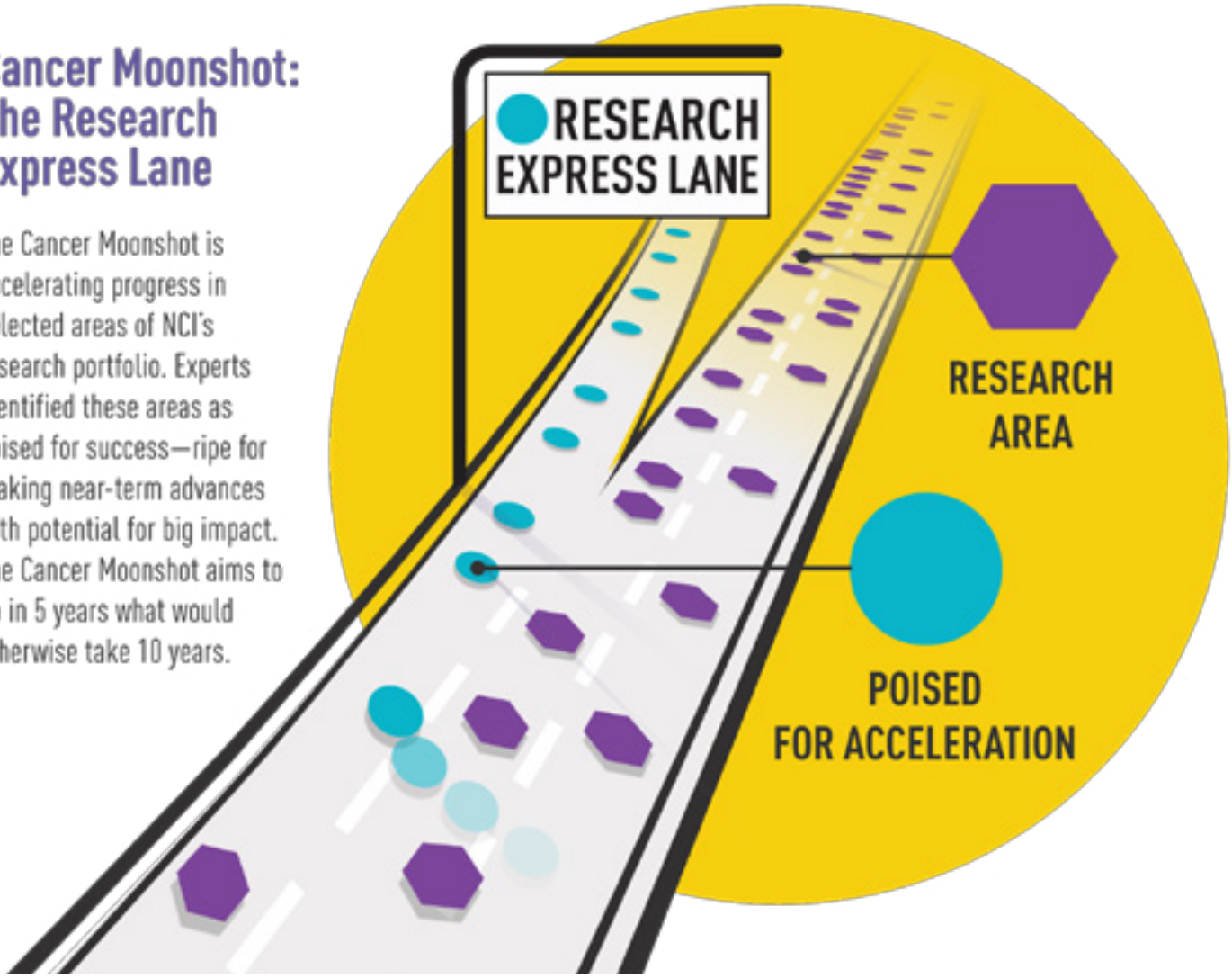
In December 2016, Congress passed the 21st Century Cures Act, authorizing $1.8 billion in funding for the Cancer Moonshot over 7 years. An initial $300 million was appropriated in fiscal year (FY) 2017 to fund the Moonshot recommendations.

CANCER MOONSHOT RECOMMENDATIONS

A. Establish a network for direct patient involvement
B. Create a translational science network devoted exclusively to immunotherapy
C. Develop ways to overcome cancer's resistance to therapy
D. Build a national cancer data ecosystem
E. Intensify research on the major drivers of childhood cancers
F. Minimize cancer treatment's debilitating side effects
G. Expand use of proven cancer prevention and early detection strategies
H. Mine past patient data to predict future patient outcomes
I. Develop a 3D cancer atlas
J. Develop new cancer technologies

Cancer Moonshot: The Research Express Lane

The Cancer Moonshot is accelerating progress in selected areas of NCI's research portfolio. Experts identified these areas as poised for success—ripe for making near-term advances with potential for big impact. The Cancer Moonshot aims to do in 5 years what would otherwise take 10 years.



KEY TAKEAWAYS

- As the largest funder of cancer research in the world, NCI invests in research ranging from basic science to clinical trials to population research to advance scientific knowledge and help all people live longer, healthier lives.
- These investments have led to improved cancer prevention, detection, and treatment methods and declines in the rates of cancer incidence and death in the United States.
- Strong and sustained support for cancer research is necessary to make advances against this disease, both in the United States and worldwide.
- Increased investments in cancer research will enable us to make even greater progress.

UNDERSTANDING THE MECHANISMS OF CANCER

Cancer is a complex disease that requires an in-depth understanding of how genetic, behavioral, and environmental factors contribute to its development. Discoveries in basic scientific research about the growth, survival, and spread (metastasis) of cancer cells in the body have been, and continue to be, essential for continued progress. Part of NCI's mission is to support the basic scientific research that will lead to new ways to prevent, detect, and treat cancer, thereby enabling people to live longer, healthier lives. Two areas of research opportunity are understanding and therapeutically targeting the molecular drivers of cancer and understanding and finding ways to control cancer metastasis.

Identifying Molecular Changes That Drive Cancer

From the time scientists began to identify cancer-causing genes, or oncogenes, in humans more than 30 years ago, they began to explore the possibility that targeting the proteins produced by these genes might kill cancer cells or slow their growth. NCI-supported basic and clinical research validated this approach, ultimately leading to Food and Drug Administration (FDA) approval of drugs such as trastuzumab (Herceptin®), imatinib mesylate (Gleevec®), and cetuximab (Erbitux®). NCI-supported research also led to FDA-approvals of drugs, such as bortezomib (Velcade®), everolimus (Afinitor®), and dinutuximab (Unituxin®), that target other molecules in cancer cells besides the proteins produced by oncogenes.

Currently, more than 35 molecularly targeted therapies have been approved by FDA for use by cancer patients. Despite this progress, more research is needed to understand the mechanisms that drive cancer. This research will help to identify additional molecular targets, to generate "lead compounds" that act against those targets, and to advance candidate drugs through the preclinical and clinical development processes.

In addition, more research is needed to understand the mechanisms by which cancer cells develop resistance to cancer therapies, including molecularly targeted therapies, and how to overcome this resistance. Drug resistance is one of the main causes of cancer treatment failure and reduced survival for patients.

THE VISION

To have effective targeted drugs to offer patients for all molecular drivers of cancer

THE APPROACH

- Support a robust research program in the molecular understanding of cancer to identify new targets
- Advance drug discovery to tackle difficult-to-target molecules

Research Priorities

NCI is committed to increasing our fundamental knowledge of the inner workings of cancer cells to identify new molecular targets and to translate those discoveries into therapies that will improve the lives of cancer patients.

Discover New Molecular Targets

The genomics revolution and technological advances that followed the completion of the Human Genome Project have allowed researchers to molecularly characterize many human cancers. One important, recently completed initiative was The Cancer Genome Atlas (TCGA), in which the genomes of more than 30 types of cancer were characterized to identify genetic alterations in the cancer cells that might be targeted therapeutically. TCGA researchers identified thousands of genetic alterations, including many potential targets. FDA-approved drugs exist for some of these targets, and additional drugs that target other genetic alterations are in various stages of development.

NCI-funded scientists are working to fully understand the role of these genetic alterations in cancer development and progression, identify ways of targeting them, develop new molecularly targeted therapies, and, ultimately, test the therapies in clinical trials to determine whether they will benefit cancer patients.

Specific NCI-supported initiatives and programs in this area include:

- The **Therapeutically Applicable Research to Generate Effective Treatments (TARGET)** initiative, which focuses on identifying molecular targets in several aggressive hard-to-treat childhood cancers. TARGET investigators have made many novel discoveries, including the identification of a distinct molecular subtype of pediatric acute myeloid leukemia that may respond to treatment with drugs called JAK kinase inhibitors. (Learn more about the TARGET initiative on page 55.)

- The **Cancer Target Discovery and Development Network (CTD²)**, in which researchers seek to functionally validate discoveries made in large-scale genomic studies that, upon further investigation, may lead to the development of new therapies. This validation may involve molecular and biological assays or computational analysis.

- The **Developmental Therapeutics Program (DTP)**, which provides services and resources to academic and private-sector researchers worldwide to facilitate the discovery and development of new cancer therapies. Since its inception by Congress in 1955, DTP has supported the development of more than 40 U.S.-licensed cancer drugs through extensive collaborations with academic institutions and pharmaceutical and biotechnology companies.

- The **NCI Experimental Therapeutics Program (NExT)**, a DTP effort that seeks to translate breakthrough discoveries in basic and clinical research into new cancer therapies while shortening the timeline for drug development. Both CTD² and NExT are intended to complement the drug development efforts of pharmaceutical and biotechnology companies by supporting meritorious, high-risk research. Dabrafenib

(Tafinlar®), trametinib (Mekinist®), and nivolumab (Opdivo®) are examples of FDA-approved drugs that were developed with the support of NExT.

Target Difficult-to-Drug Molecules

Although we have successfully developed therapies that target the proteins produced by many oncogenes, there is still much work to be done. For example, members of the *MYC* and *RAS* gene families are frequently altered in human cancer, but drugs that directly target their protein products have yet to be approved by FDA.

- The ***RAS* gene family** includes the genes *HRAS*, *KRAS*, and *NRAS*. Mutations in these genes cause more than 30% of all human cancers, including 95% of pancreatic cancers and 45% of colorectal cancers. Cancers that have a *RAS* mutation generally have a poor prognosis. Developing drugs that effectively target mutant RAS proteins is a major research challenge. In one such effort, NCI-funded researcher Kevan Shokat, Ph.D., of the University of California, San Francisco, generated small molecules that target a specific alteration in KRAS. (Read about Kevan's work on page 16.)

  In 2013, NCI launched the RAS Initiative to accelerate progress in this area. Under this initiative, researchers are exploring innovative approaches to target *RAS*-driven cancers, with the goal of finding effective therapies for patients with these cancers. Based at the Advanced Technology Research Facility of NCI's Frederick National Laboratory for Cancer Research, the initiative brings together scientists from NCI's intramural research program, academia, and biotechnology and pharmaceutical companies. The RAS Initiative highlights NCI's ability to convene experts from across the research enterprise to address complex problems in cancer research.

- The ***MYC* family of genes**, which was discovered decades ago and includes the *MYC*, *MYCN*, and *MYCL* genes, has been shown to be a critical player in the development of approximately 15% of human cancers and in drug resistance to targeted therapies. Despite this knowledge, no drug has been developed that targets MYC proteins directly. However, recent work by NCI-funded researchers and others has led to the discovery of a promising new class of dual-action inhibitors that block the activity of two other proteins, BRD4 and PI3K, that are necessary for the activation and stabilization of MYC proteins.

This work and other recent advances in the drug discovery field have renewed enthusiasm for our ability to hit targets that once were thought to be "undruggable."

KEY TAKEAWAYS

- NCI supports research to understand the molecular basis of cancer and to identify molecules in cancer cells that are potential therapeutic targets.
- NCI supports research to develop molecularly targeted therapies for cancer, including therapies that target yet-to-be-drugged molecules.

KEVAN SHOKAT, PH.D.

Professor, Department of Cellular and Molecular Pharmacology, University of California, San Francisco

Professor, Department of Chemistry, University of California, Berkeley

Investigator, Howard Hughes Medical Institute

THINKING CHEMICALLY TO DISCOVER NEW TARGETED CANCER DRUGS

Chemical biologist Kevan Shokat brings a unique perspective to the development of molecularly targeted therapies. He began his research career as an organic chemist, only later turning to biology. He believes that this hybrid training enables him to "think chemically" but with a deep enough understanding of biology to know what to focus on in addressing major biomedical challenges. Importantly, he believes we need to unwind many of our assumptions about things and conduct research in an open-minded, open-ended way. "That will lead us to fundamental discoveries," he said, "and, every so often, you'll overturn some dogma and that will be the crack in the problem."

Encouraged by pioneers in the study of oncogenes—altered genes that have the potential to cause cancer—Kevan entered the field of cancer drug discovery. Among the oncogenes he sought to target were members of the *RAS* gene family, which play an important role in more than 30% of all human cancers, including 95% of pancreatic cancers, 45% of colorectal cancers, and 35% of lung cancers. The proteins produced by *RAS* oncogenes had long been thought to be "undruggable" because they lack a clear binding site for drug attachment. Kevan, however, prefers to view them as "not yet drugged."

With the support of NCI funding, Kevan's team focused initially on a mutant form of the *KRAS* gene that occurs in non-small cell lung cancer. Using a technology that had not previously been applied to oncogenes, they successfully inhibited the protein by chemically binding, or tethering, small molecules to the part of the protein that was altered by mutation. Additional research showed, however, that these small molecules bound to what was thought to be an inactive form of the protein. Before this finding, it had been universally accepted that mutant RAS proteins were locked in an active state and that successful RAS inhibitors would target that active state. Not only were these two long-standing beliefs overturned by this research, further research would show that cancer-causing mutants in a RAS-related protein, which was supposedly in its inactive state, actually exists in the active state.

"Many of the assumptions we've made, about proteins we've studied a lot in cancer, are wrong," Kevan said, "and these assumptions are hindering our ability to make discoveries." He believes that findings like these underscore the need for more basic research. He also said that it is very important for NCI to sustain funding for cancer drug discovery aimed at high-value targets, such as *RAS*, and even to prioritize high-risk, high-reward science. "We don't have enough discoveries on the table to add them up in different ways to construct the next major drug," he said. "We need more discoveries."

Learning How Cancer Spreads and How to Stop It

In the future, clinicians will be able to accurately predict whether a given cancer will spread (metastasize) to another part of the body. Treatments tailored to the individual patient to prevent or block metastasis will also be possible. Before that day can come, however, we must acquire a deeper understanding of how cancer spreads and thrives in new locations. Although great progress has been made over the last two decades in the treatment of cancer, metastasis remains cancer's most lethal aspect.

The "seed and soil hypothesis" of cancer metastasis was proposed more than 125 years ago. In this hypothesis, successful metastasis occurs only when distant organs and tissues (the "soil") are suitably hospitable to cancer cells (the "seeds") to allow them to survive and grow into new tumors. Although this basic premise still holds, metastasis is now known to be more complex than just a seed finding suitable soil. The type of cancer, the ability of the spreading cells to survive in the circulatory system, and the organ or tissue to which they spread all influence how the metastatic process unfolds.

Another important factor is when cancer cells spread. For many years, it was thought that metastasis occurred late in tumor development, but recent evidence indicates that cancer cells can spread throughout the body before the development of a palpable tumor. For example, using a mouse model of breast cancer, NCI-funded researchers were able to show that cancer cells can spread from a tumor even before the tumor is large enough to be detected. In addition, the cells that spread early were more likely to give rise to metastatic tumors than cells that spread later in tumor development.

These findings have implications for the early detection and treatment of metastatic tumors. However, many unanswered questions remain, and additional research is needed to make progress for patients.

THE VISION

To prevent or significantly delay the lethal outcome of metastatic cancer

THE APPROACH

- Support research to increase our understanding of the metastatic process, including the timing of events that lead to metastatic disease and where in the body metastasis occurs
- Develop cellular and animal models that faithfully represent the metastatic process in humans

Research Priorities

NCI supports research that investigates all aspects of the metastatic process, from how tumor cells metastasize to why certain cancer types colonize some organs and not others.

Understand How Distant Tissues Are Conditioned for Metastatic Colonization

The local environment in an organ or tissue where a metastatic tumor will eventually grow is not a passive player in the process of metastasis. NCI-funded researchers have shown that this environment must first be conditioned to create a hospitable neighborhood—termed a premetastatic niche—before the spreading tumor cells arrive.

Subsequent discoveries have shown that tumors play an active role in creating this niche by, among other things, sending out tiny messengers called exosomes. Tumor cell exosomes contain cellular components, such as DNA and proteins, wrapped up in a piece of the tumor cell's outer membrane. They transport their contents through the body's circulatory system to help condition distant locations for metastatic colonization. NCI-funded researchers are exploring the use of exosomes and other tumor-secreted vesicles as biomarkers and potential therapeutic targets for predicting and preventing metastatic disease. (Read about one of these researchers, David Lyden, M.D., Ph.D., of Weill Cornell Medical College, on page 20.)

Another area of investigation is understanding why specific cancers preferentially metastasize to certain organs or tissues but not to others. For example, breast and prostate cancers often metastasize to the bones, and gastrointestinal cancers frequently metastasize to the lungs and liver. The factors underlying this tissue-specific predisposition for metastasis are largely unknown and are being studied by the cancer research community. Identifying these factors may reveal strategies to limit metastatic disease.

Investigate When Metastasis Occurs

Cancer cells that have spread from a tumor to a distant location may grow to form a new tumor, die, or become dormant. Some cancer cells can remain dormant for 5, 10, or even 20 years before they begin to divide again and form a metastatic tumor. Advances in technology have made it possible to study this phenomenon, called metastatic dormancy, by tracking single cells in animal models and characterizing them at the molecular level. In one example, NCI-funded researchers identified a specific gene signature as a potential biomarker of dormancy in single disseminated prostate cancer cells isolated from the bone marrow of patients. Whether this biomarker can be used to monitor early recurrence in prostate cancer patients is being explored.

Develop Models to Understand Metastasis

Achieving a better understanding of cancer metastasis will require new approaches and models to study the process and how it affects patients. Some NCI-supported programs and initiatives designed to address these needs include the following:

- The **Oncology Models Forum,** which is a platform for scientists to share information about animal models, including information about generating, validating, and credentialing new mouse models. In addition, patient-derived xenograft (PDX) mouse models have generated excitement due to their ability to better predict responses to treatment, and, as they are refined, they may prove useful in metastasis research.

- The **Provocative Questions Initiative**, through which new approaches to studying metastasis are being developed with NCI support. NCI has funded seven metastasis-related research projects under this initiative, including one to develop a metastasis-on-a-chip assay. Although this assay is still in the early stages of testing, it has the potential to be used for studying how metastatic cells migrate and, ultimately, for testing drugs to inhibit the metastatic process.

- The **Cancer Systems Biology Consortium**, which integrates biology, mathematics, computer modeling, and engineering technology to further advance studies of the complexity of cancer. One of the nine academic centers in the consortium focuses specifically on cancer metastasis, and other consortia members study various aspects of metastasis.

KEY TAKEAWAYS

- NCI supports fundamental research in cancer metastasis to develop ways to prevent or block metastasis and better treat patients with metastatic disease.
- This research includes studies to increase our understanding of how tumor cells colonize distant organs or tissues, why they preferentially spread to certain sites, and what controls the timing of metastatic spread.
- NCI also supports the development of models that better represent the metastatic process in humans.

DAVID LYDEN, M.D., PH.D.

Stavros S. Niarchos Chair, Weill Cornell Medical College

Pediatric Neuro-Oncologist, Memorial Sloan Kettering Cancer Center

SHINING A SPOTLIGHT ON THE EXOSOME

Metastasis causes about 90% of deaths from cancer. Understanding how cancer spreads throughout the body could reveal new opportunities to curtail tumor growth and help prolong the lives of cancer patients. Pediatric neuro-oncologist and researcher David Lyden is an NCI-funded scientist who has worked arduously for nearly two decades to uncover the steps of cancer cell metastasis.

David's research focuses on exosomes, tiny sac-like structures, or vesicles, that are secreted by cells and circulate in the blood. Until recently, researchers had largely ignored exosomes and believed that tumor cells alone initiate metastasis at distant sites. However, David and his team discovered that, long before cancer cells arrive at a distant site, tumor exosomes help create a nurturing, or conditioned, environment for metastatic tumor growth. Through this and other work, they demonstrated that a primary tumor actively prepares so-called premetastatic niches in the body.

An unanswered question in metastasis research is why certain cancers preferentially metastasize to specific sites. For example, lung cancers often spread to the brain, and prostate cancers regularly spread to the bones. Expanding on their previous findings, David's team made a discovery that sheds light on these patterns. "We saw that integrins, specific proteins on the surface of exosomes, direct where the exosomes will travel in the body," he said. "We think of them as a molecular zip code."

For example, one exosome might have integrins on its surface that bind to specific cells in the liver, thereby mediating metastasis to the liver, whereas another exosome might have integrins on its surface that bind to cells in the lungs, thus facilitating lung metastasis. Once the exosomes have reached their destination, they initiate local changes that help support the growth of future tumors.

This pioneering work—discovering the premetastatic niche and demonstrating the critical role of tumor exosomes—has ignited a new field of research. The number of scientists studying tumor exosomes has swelled from several dozen in 2012 to more than a thousand in 2017. They are increasing our understanding of exosome biology and hope to use this information to develop new ways to detect and treat cancer.

David is very passionate about the future of exosome research and is adamant that the goal of biological studies should be to help patients. "This research could help physicians identify patients whose tumors are not likely to metastasize, and thus help them avoid unnecessary treatment." He thinks it could be possible to identify sites of future metastasis by tagging exosomes from a patient's tumor and following them with imaging technologies. Furthermore, he wonders if blocking tumor exosome production may lead to better patient outcomes and fewer deaths due to metastasis.

PREVENTING CANCER

Cancer prevention has the potential, in the long run, to save even more lives than treatment. With improved prevention, fewer people would face a diagnosis of cancer and the physical, financial, social, and psychological harms of the disease and its treatment.

NCI's support of cancer prevention research is particularly critical because the private sector is generally not incentivized to make prevention a priority due to the many economic, logistical, and scientific challenges that must be overcome. For example, most cancers are rare diseases that develop slowly over many years, or even decades. Therefore, clinical trials testing the effectiveness of new cancer prevention methods require very large numbers of patients and years to conduct.

Although new cancer prevention interventions are greatly needed, full implementation of existing evidence-based approaches would greatly reduce the burden of cancer in the United States. Research suggests that more than half of all cancer deaths that occur in this country each year could be prevented if people quit smoking, drank only moderate amounts of alcohol, maintained a healthy body weight, exercised regularly, and received recommended cancer screenings and vaccinations.

Current NCI-supported cancer prevention efforts focus on:

- Reducing exposure to cancer-causing agents in the environment, such as tobacco smoke, ultraviolet radiation, asbestos, arsenic, and radon gas.
- Cancer screening tests, such as the Pap smear for cervical cancer and colonoscopy for colorectal cancer, which can detect precancerous growths that can be removed or destroyed before they progress to cancer.
- Vaccinations against cancer-causing viruses, such as the hepatitis B virus and high-risk types of human papillomavirus, to prevent persistent infections that lead to the development of cancer. About 10% of all cancers are caused by viruses.

An emerging area of opportunity is the development of vaccines to prevent not only the cancers that are caused by viruses but also cancers that are not caused by viruses.

Developing Vaccines to Prevent Cancers Not Caused by Viruses

We now have safe and effective vaccines against several viruses that cause cancer, but can vaccines be developed for cancers that are not of viral origin? That is the goal of NCI-funded researchers who are aiming to use the power of the immune system to prevent cancers that are not caused by viruses.

Vaccines are excellent noninvasive, immune-based interventions to prevent cancer. They usually have fewer side effects than chemoprevention agents, such as tamoxifen for breast cancer prevention, and do not require regular use over many years. In addition, the immune system has a memory. This means that vaccination will produce a reservoir

of immune cells that remember a threat to the body and can spring into action if that threat is encountered again.

For many years, researchers have been trying to make vaccines to treat patients with cancer. Now, they think it may be possible to make vaccines that will prevent certain cancers from occurring at all or prevent already treated cancers from recurring.

THE VISION

To develop safe and effective vaccines that prevent cancers not caused by infectious agents

THE APPROACH

- Support research to identify, characterize, and test candidate antigens for vaccine development
- Enable the development of cancer prevention vaccines through preclinical and clinical research

Research Priorities

To advance cancer prevention, NCI supports a range of basic, translational, and clinical research necessary for vaccine development.

Support Research to Identify and Characterize Candidate Tumor Antigens

NCI supports research to identify and characterize tumor antigens, which are parts of proteins on cancer cells that can trigger an immune response. Tumor antigens that trigger the strongest immune responses may become part of vaccine formulations for cancer prevention and treatment.

In addition to supporting investigator-initiated research in this area, NCI is launching an effort called the **Pre-Cancer Atlas (PCA)**, in which large numbers of precancerous growths and early cancers will be systematically collected, catalogued, and analyzed comprehensively to understand how different types of cancer arise and progress. The creation of this atlas, which will include imaging, genomic, proteomic, and other types of data, will be accelerated greatly by the Cancer Moonshot℠. Characterizing the changes that occur in the cells of precancerous growths and early cancers should enable the identification of potential targets for early intervention, including the development of vaccines. (Learn more about PCA on page 32.)

Facilitate the Development of Cancer Prevention Vaccines

NCI programs that support vaccine development include:

- NCI's **PREVENT Cancer Preclinical Drug Development Program**, which supports early- and late-phase preclinical drug development needs that are not being adequately addressed by the private sector. This program is currently supporting

work on several prevention vaccines, including one to prevent colorectal cancer in people with Lynch syndrome, a hereditary condition that increases the risk of colon and several other types of cancer. People with Lynch syndrome have a defect in their DNA repair machinery that results in recurrent mutations at specific protein-coding locations in the genome. The mutant proteins stemming from these mutations are being investigated as targets for vaccine development.

- NCI's **Phase 0/I/II Cancer Prevention Clinical Trials Program**, which supports early clinical development of promising prevention agents. To date, 22 trials have been supported. One of these trials is a randomized phase II clinical trial of a vaccine targeting the tumor antigen MUC1 to prevent colorectal cancer. Abnormally modified MUC1 protein is produced by the cells of advanced adenomas, which are precancerous polyps in the colon. (Learn more about NCI-supported research on this vaccine in the story about Olivera Finn, Ph.D., of the University of Pittsburgh, on page 26.)

KEY TAKEAWAYS

- NCI supports a wide range of cancer prevention research, including the development of vaccines to prevent cancers not caused by viruses.
- One near-term goal of this research is to demonstrate that these vaccines can safely and effectively prevent cancer recurrence.
- A longer-term goal is the development of vaccines to prevent multiple types of human cancer.

OLIVERA FINN, PH.D.

Distinguished Professor, University of Pittsburgh

PURSUING A CANCER PREVENTION VACCINE

For more than two decades, Olivera Finn has tirelessly pursued one goal in her research: to develop a vaccine to prevent cancer. She has had this goal since 1989, when her research team discovered the first tumor antigen recognized by a type of immune cell that can kill cancer cells. That antigen—an abnormal version of a protein called MUC1—is produced by the cells of more than 80% of cancer types, including cancers of the breast, pancreas, colon, lung, and prostate.

Although she started her research career as an organ transplant immunologist, the discovery of MUC1 was a pivotal point in Olivera's career trajectory. "Once we discovered tumor antigens," she said, "I never looked back." Olivera received her first NCI grant in 1991 and has been funded ever since to study the biology of tumor antigens and develop them as targets for cancer prevention.

Cancer can take many years—even decades—to develop. Some cancers arise from precursor growths that can be detected by current screening methods. For example, colorectal polyps called advanced adenomas, which can be detected by colonoscopy, can progress to colorectal cancer. These adenomas can be removed surgically, but in many patients, new ones continue to develop and some will become malignant. Olivera's lab found that the cells of advanced adenomas and the precursors of pancreatic, lung, and many other types of cancer all produce abnormal MUC1 protein.

The presence of abnormal MUC1 on premalignant growths may make it a good target for a vaccine that would prevent their progression to cancer or the development of new precursors. To test this idea, Olivera's group conducted the first ever clinical trial of a cancer prevention vaccine based on a tumor antigen in healthy people without cancer who were at increased risk of developing the disease.

In the NCI-funded trial, reported in 2013, individuals with a history of advanced adenomas were given an MUC1 vaccine. The vaccine was shown to be safe and to elicit a strong immune response and a long-lasting immune memory. NCI is currently sponsoring a phase II trial testing whether the vaccine will prevent the regrowth of colorectal polyps.

Looking forward, Olivera envisions, "If you are in your 60s and your doctor discovers you are at high risk for cancer, the idea would be to vaccinate to boost the immune system's ability to keep any abnormal cells in check instead of waiting to see if cancer develops."

Olivera says that funding from NCI is critical for her research and for cancer prevention research in general. Cancer prevention research is complex, and translating laboratory discoveries into new ways to prevent cancer requires sustained investments over many years—investments that the private sector is often reluctant to make. But "building the evidence that vaccines are an effective way of controlling cancer will go a long way toward getting companies interested," she said.

The field of cancer immunology has expanded dramatically and has led to immunotherapies for the treatment of advanced cancers as well as vaccines against some viruses that cause cancer. Boosting the immune system to prevent cancers that are not caused by viruses may now be within reach. "The opportunities are amazing," she added.

Preventing Virus-Associated Cancers

More than 2 million cancers worldwide each year are caused by 10 different infectious agents. Seven of these agents are viruses, including the human papillomavirus (HPV, of which there are 13 high-risk types), the hepatitis B virus (HBV), the hepatitis C virus (HCV), and the Epstein-Barr virus (EBV).

The HPV vaccines that are currently available are highly effective in preventing the development of high-grade cervical lesions, which are precursors to cervical cancer that are caused by persistent infections with high-risk HPV types. Because the same HPV types (16 and 18) that cause about 70% of all cervical cancers also cause most cases of vaginal, vulvar, anal, penile, and oropharyngeal cancers, immunization may reduce the incidence of these cancers as well.

Despite the ready availability of HPV vaccines in the United States, vaccination rates remain low. These low vaccination rates stand in sharp contrast with the vaccination rate for another cancer prevention vaccine, the HBV vaccine. HBV is a major cause of liver cancer, and vaccination against this virus is nearly universal in this country.

THE VISION

To prevent the ability of viruses to cause cancer through the development and widespread application of additional vaccines

THE APPROACH

- Broaden the prevention of HPV-associated cancers
- Develop new vaccines against additional viruses that cause cancer

Research Priorities

Additional NCI-funded research will build on efforts against HPV-associated cancers and focus on other cancers that have viral causes.

Broaden the Prevention of HPV-Associated Cancers

NCI efforts against HPV-associated cancers include the following:

- NCI is sponsoring a clinical trial to assess the efficacy of immunization with one dose of HPV vaccine. This research builds on previous NCI-led research that showed that two doses of HPV vaccine were as effective as three doses, a finding that changed national vaccine guidelines for younger adolescents. The finding that two doses is sufficient for this group is important because administering fewer doses is logistically simpler and more cost effective, which is especially important in resource-poor areas. One dose would further reduce costs and improve vaccine uptake, thereby having a greater impact on preventing cervical and, possibly, several other types of cancer.

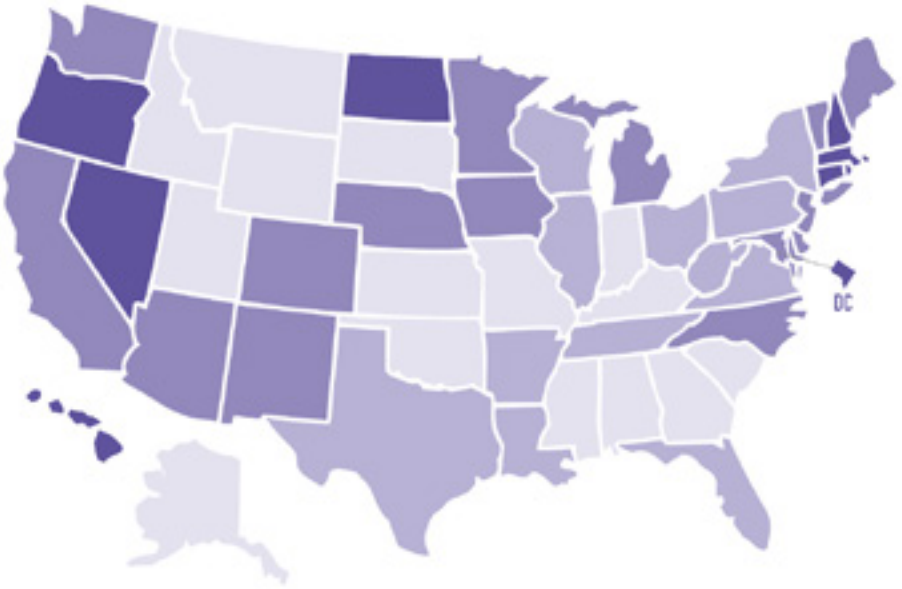
Improving HPV Vaccination Rates Will Help Save Lives

NATIONWIDE
6 OUT OF 10
GIRLS HAVE STARTED THE HPV VACCINE SERIES

National coverage is 63%
Coverage by state:

- 59% or less
- 60–64%
- 65–69%
- 70% or greater

Percentage of Adolescent Girls Who Have Received One or More Doses of HPV Vaccine*

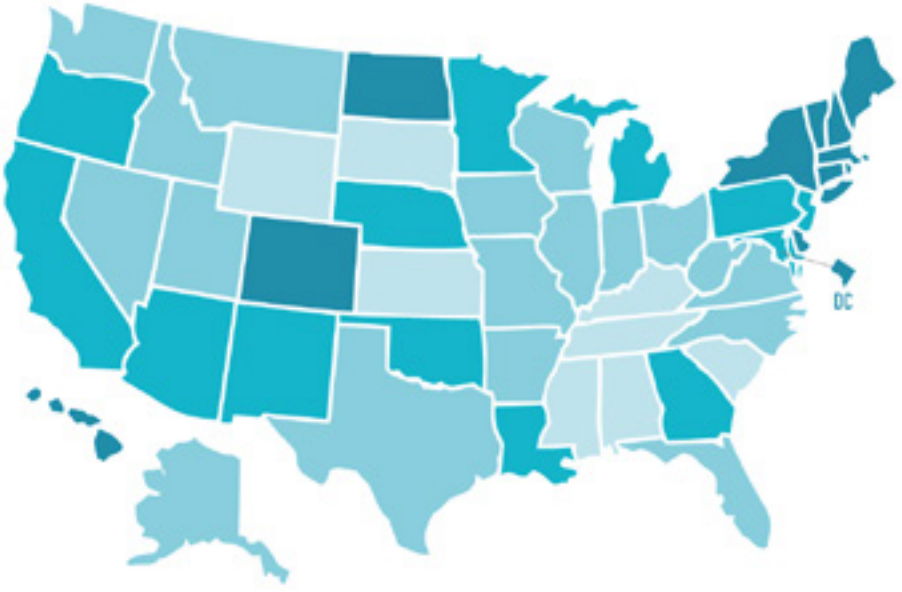


NATIONWIDE
5 OUT OF 10
BOYS HAVE STARTED THE HPV VACCINE SERIES

National coverage is 50%
Coverage by state:

- 39% or less
- 40–49%
- 50–59%
- 60% or greater

Percentage of Adolescent Boys Who Have Received One or More Doses of HPV Vaccine*



HPV VACCINATION IS THE BEST WAY TO PREVENT SEVERAL TYPES OF CANCER. YET MANY ADOLESCENTS HAVE NOT STARTED THE HPV VACCINE SERIES.

*Estimated coverage with ≥1 dose of human papillomavirus (HPV) vaccine among adolescents age 13-17 years [Source: National Immunization Survey—Teen, United States, 2015]

Source: *MMWR* August 26, 2016

- HPV vaccines work best when given before a person is exposed to the virus. For women already exposed and at risk of cervical cancer, NCI-supported researchers are trying to develop vaccines against virus antigens associated with HPV-induced cancers. These antigens include the HPV proteins E6 and E7. Vaccines targeting these antigens may prevent high-risk precancerous growths from progressing to cervical cancer.

Develop New Prevention Methods against Additional Cancer-Causing Viruses

The successful production of vaccines against additional viruses that cause cancer will have tremendous global impact. For example, Epstein-Barr virus (EBV) infections cause an estimated 200,000 new cases of cancer each year worldwide. Vaccines against EBV, which causes Burkitt lymphoma, some types of Hodgkin and non-Hodgkin lymphoma, and about 10% of gastric (stomach) cancers, are in development. NCI also supports research that is essential to understanding how EBV interacts with other risk factors to drive cancer development and to find other ways to intervene to prevent EBV-associated cancers.

KEY TAKEAWAYS

- NCI is supporting research to broaden the use of currently available vaccines against cancer-causing viruses.
- NCI is also supporting research to develop additional vaccines against the currently targeted viruses and other cancer-causing viruses.
- The ultimate goal of this research is to prevent cancer caused by viruses.

DETECTING & DIAGNOSING CANCER

Early detection is a proven strategy for saving lives from cancer. The early detection of cancer greatly increases the chances of successful treatment. Far too often, however, cancers are diagnosed at later stages, when curative treatment is no longer possible.

The best scenario would be to have the ability to identify precancerous growths that are destined to become life-threatening cancers, providing the opportunity for early intervention to prevent cancer from developing altogether. Moreover, the ability to accurately identify abnormal growths that will not progress to potentially fatal cancers would spare patients the physical and financial harms of unnecessary treatment and the psychological harms of a cancer diagnosis.

Areas of opportunity include developing new approaches, including liquid biopsies and other less-invasive methods, for the early detection of precancers and early cancers. These approaches have the potential to increase the number of cancers for which we have clinically effective screening programs as well as improve the technologies currently used to screen for cancer.

Improving Early Detection to Reduce the Burden of Cancer

Reliably detecting cancer at the earliest possible stage, regardless of where it occurs in the body, and accurately identifying people who are at increased risk of cancer are high-priority goals for NCI.

THE VISION

To accurately and reliably detect precancerous growths and early cancers wherever they are in the body, thus enabling timely intervention as needed to prevent these abnormal growths from becoming life-threatening cancers

THE APPROACH

- Support research to understand how precancerous growths develop and progress (or not) to cancer and to identify biomarkers for risk prediction and early detection
- Improve existing methods for early detection and develop new, noninvasive technologies to accurately and reliably detect precancerous growths and early cancers

Research Priorities

More research is needed to understand how precancerous growths progress to cancer and how to translate this knowledge into new and improved technologies for early cancer detection.

Understand How Precancers Progress to Cancer

NCI supports studies to understand the molecular events that occur during the transition from precancerous growths to malignant tumors. This research will lead to new methods to detect cancer early, enable better treatment decisions, and improve cancer prevention. To address these goals, specific NCI programs include:

- NCI's **Consortium for Molecular and Cellular Characterization of Screen-Detected Lesions**, which supports multidisciplinary research at 15 different institutions across the country on the molecular and cellular features of cancerous and precancerous tumors that have been detected by a cancer screening test. This research, which was initiated in 2015, will provide information to help distinguish screen-detected tumors that are indolent (nongrowing or slow-growing) from those that are aggressive and, therefore, need immediate treatment. The ultimate goal of this research is to help doctors and patients decide whether treatment is warranted or whether regular monitoring, with the possibility of later treatment, is sufficient.

- NCI is also launching a **Pre-Cancer Atlas (PCA)** program to systematically collect, catalogue, and analyze large numbers of precancerous growths and early cancers to understand how different types of cancer arise and progress. This effort will be greatly accelerated by the Cancer Moonshot℠. Information collected through the PCA program will enable the development of more sensitive early detection methods. In addition, PCA research will advance cancer prevention efforts. (Learn more about how the PCA will aid prevention research on page 24.)

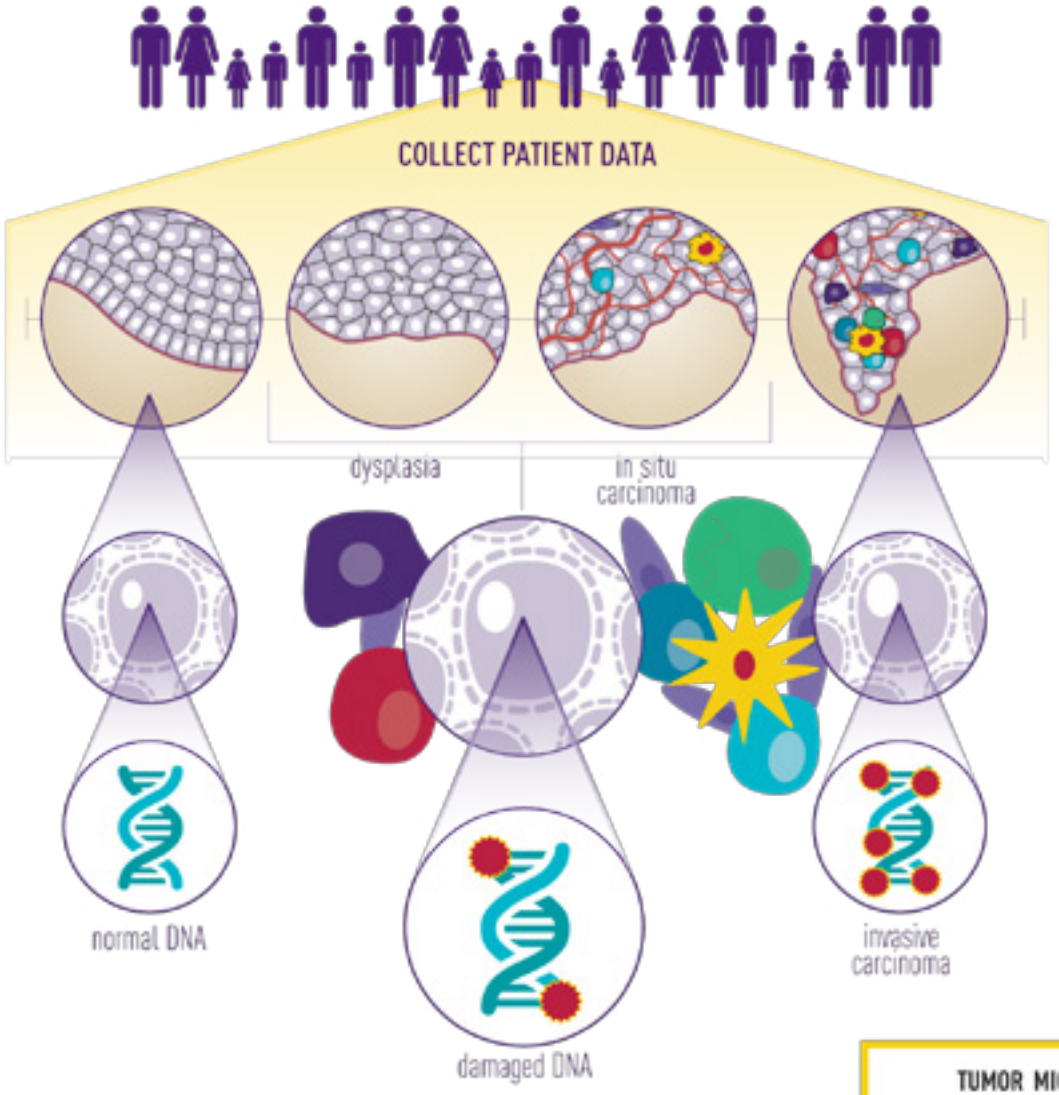
- NCI's **Early Detection Research Network (EDRN)** brings together scientists from more than 30 different institutions and organizations across the country to accelerate the identification and clinical validation of biomarkers of cancer at its earliest stages and to evaluate new methods of testing for cancer risk and early cancers. EDRN-supported research has led to Food and Drug Administration approval of a urine-based test for the detection of prostate cancer and a molecular test for the early detection of lung cancer. (Read more about the lung cancer test developed by Avrum Spira, M.D., M.Sc., of Boston University, on page 36.)

Improve Current Detection Methods and Develop New Technologies

Our increased understanding of cancer and advanced technological capabilities are amplifying opportunities for noninvasive early detection. The development of the liquid biopsy and new or improved imaging methods are examples.

- **Liquid biopsy**: Imagine if a simple blood draw in a doctor's office could be used to detect, stage, or monitor cancer. Perhaps one of the most rapidly evolving areas in cancer research is identifying and validating tumor biomarkers in blood, urine, sputum, or other bodily fluids. Investigators, including many supported by NCI, have discovered that cancer cells and molecules released from them (such as DNA and RNA) can be detected in these fluids. The process of collecting samples of bodily fluids, known as a liquid biopsy, is simple, minimally invasive, and can be repeated on a regular basis. This approach stands in stark contrast with standard

Pre-Cancer Atlas



UNDERSTANDING WHY PRECANCEROUS TISSUE TURNS INTO CANCER

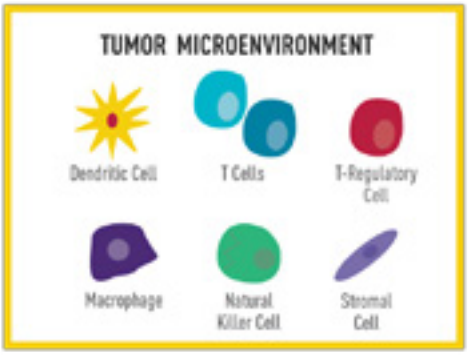
If we understood and could predict which precancerous cells will turn into cancer, we could develop targeted interventions to prevent cancer from forming.

Through the Pre-Cancer Atlas (PCA) initiative, NCI will systematically collect precancerous tissues; analyze their genomes and tumor microenvironments; and compare their molecular features to data collected on thousands of other patient outcomes to develop a predictive model of when cancer develops.

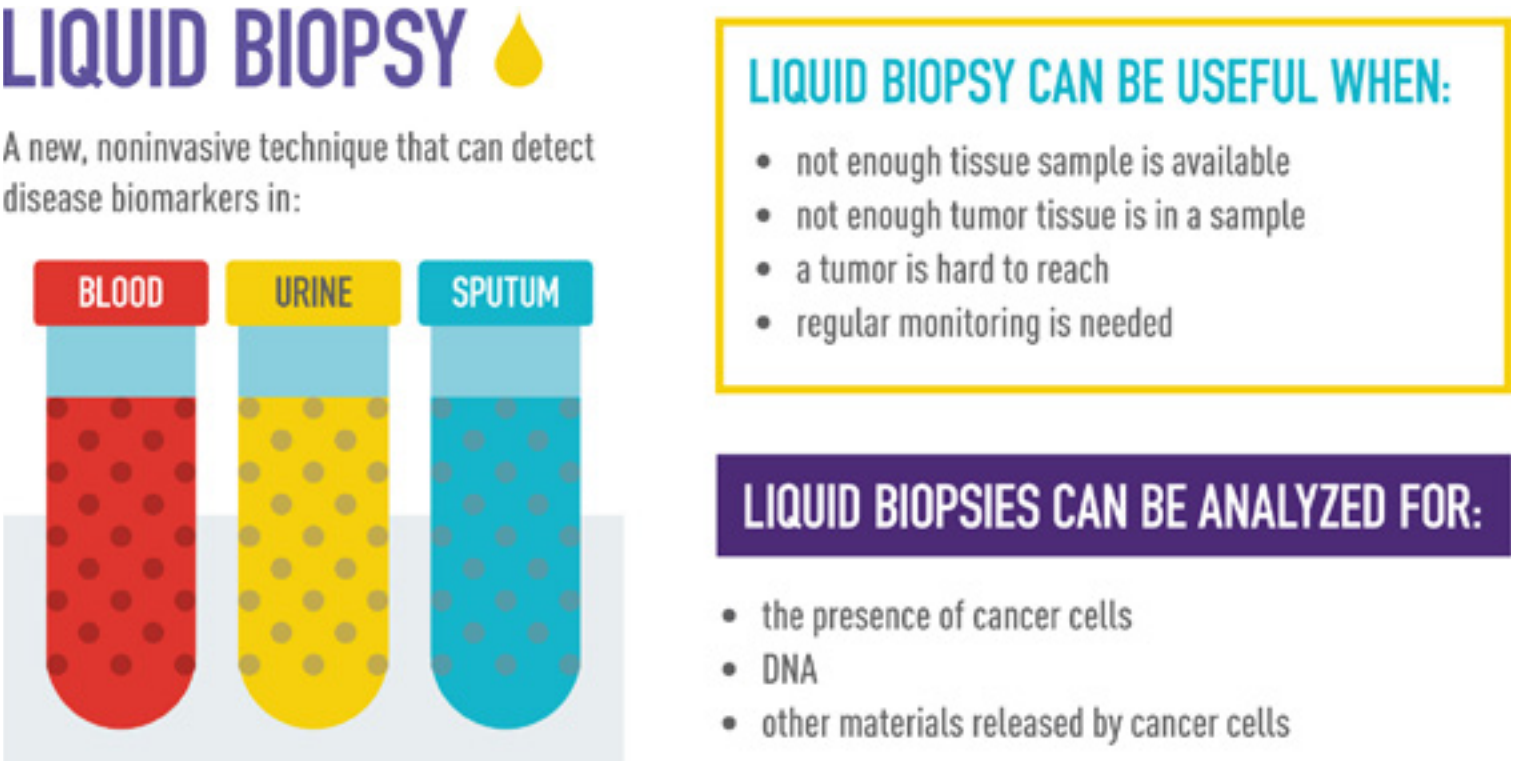
The PCA will build on the technology infrastructure of The Cancer Genome Atlas initiative, which collected 2.5 petabytes of genomic data on samples collected from 11,000 patients with 33 different tumor types. Since precancers are more common, the PCA will require additional technology infrastructure to collect more types of data from an even greater number of patients.

ANALYZING THE DNA AND MICROENVIRONMENT OF PRECANCEROUS CELLS TO PREDICT FUTURE MALIGNANCY

At the precancer stage, cells may appear relatively normal, but advances in technology may help identify abnormalities in DNA and the microenvironment that can distinguish precancerous cells that will likely remain benign from those likely to advance to an invasive cancer.



BENEFITS OF A PRE-CANCER ATLAS



biopsy procedures, in which a tumor is sampled directly, often with surgery. However, before this new approach can become broadly useful for early cancer detection, much more work needs to be done to develop standardized methods to maximize the sensitivity (true-positive rate), specificity (true-negative rate), and reproducibility of biomarker identification in specimens of bodily fluids. This effort will require improvements in both detection technologies and methods, in addition to identifying the most appropriate biomarkers in these fluids. To address these challenges, NCI is establishing a **Precompetitive Collaboration on Liquid Biopsy for Early Cancer Assessment** to facilitate public–private partnerships to advance this technology for early detection.

- **Cancer imaging**: Biomedical imaging is important in cancer screening, diagnosis, staging, treatment, and the monitoring of disease response or recurrence. Many advances in cancer imaging have been made in recent decades, but more work remains to improve the sensitivity, specificity, and breadth of available imaging techniques. To expedite developments in this area, NCI is creating a **Consortium for Imaging and Biomarkers**, which will foster multidisciplinary collaborative research. NCI also sponsors clinical trials of new imaging methods. For example, in 2017, NCI launched the **Tomosynthesis Mammography Imaging Screening Trial (TMIST)** to compare the effectiveness of 3D digital mammography (breast tomosynthesis) and standard 2D digital mammography in detecting breast cancer and reducing the incidence of advanced tumors diagnosed.

- **Molecular analysis technologies**: There are a variety of other approaches that can be used to study precancerous growths and early cancers and to detect biomarkers of these lesions. Optimizing the utility of these approaches involves the development of improved analytical methodologies and tools. NCI's **Innovative Molecular Analysis Technologies** program has catalyzed and fostered the early-stage development of highly innovative analytical technologies and tools for nearly 20 years, and it continues to support the development of next-generation technologies that have the potential to revolutionize the way that precancerous growths and early cancers can be studied.

KEY TAKEAWAYS

- NCI is committed to identifying and validating biomarkers in liquid biopsy specimens that will allow cancers to be detected at the earliest possible stage, when treatment is likely to be most effective and patients have the greatest prospects for long-term survival.
- NCI supports the development of new and improved technologies for the noninvasive detection of precancerous growths and early cancers.
- NCI supports additional research to improve our understanding of how precancerous growths transition to cancer, which will increase opportunities for early detection and cancer prevention.

AVRUM SPIRA, M.D., M.SC.

Director, Boston University-Boston Medical Center Cancer Center

BRUSHING THE AIRWAY TO DETECT LUNG CANCER EARLIER

More people die from lung cancer than from any other cancer type. In 2017 alone, the estimated number of lung cancer deaths in the United States will exceed 155,000. Tobacco smoking is the prime culprit underlying the development of most lung cancers. Sadly, most people are diagnosed with late-stage disease that has spread to other parts of the body and is difficult to treat.

Low-dose computed tomography (CT) screening can be used to detect lung cancer at earlier stages, but false-positive results, suggesting cancer is present when it is not, are common. False-positive results mean that many people who have benign lung nodules must undergo invasive and painful follow-up tests to see if they have cancer. Having experienced the limitations of low-dose CT screening firsthand in his pulmonary practice, Avrum Spira, a physician, researcher, and entrepreneur at Boston University, was determined to change that. With NCI funding, he is transforming the paradigm of early lung cancer detection and screening.

Avrum's approach makes use of the fact that tobacco smoke wreaks havoc on the cells that line the upper airway and the lungs, causing damage to their DNA that can eventually lead to cancer. Drawing on previous ideas about how the toxins in cigarette smoke damage a much larger "field" of tissue than the precise spot where a malignant tumor will eventually grow, he reasoned that it might be possible to test samples of upper airway tissue for signs of genomic damage that are associated with lung cancer deep within the lung.

To determine whether cells in the upper airway, which are much easier to sample than cells in a lung nodule or tumor, can provide a sign that a person has cancer, he piggybacked on a minimally invasive endoscopic procedure called bronchoscopy. This procedure is often used as an initial diagnostic test for smokers and former smokers who have lesions in their lungs that are suspicious for cancer. As a stand-alone test, however, bronchoscopy misses 40%–50% of lung cancers because many nodules and tumors are beyond the reach of a bronchoscope.

To collect cells from the upper airway for analysis, Avrum and his team used a bronchoscope equipped with a brush. The collected cells were then analyzed for molecular changes associated with lung cancer. With this approach, they identified a characteristic set of genomic changes in cells from the upper airways of patients with lung cancer.

In 2007, Avrum started a company that conducted two clinical trials of this "bronchial genomic classifier" in patients who had not been diagnosed with lung cancer from 28 medical centers—26 in the United States, one in Canada, and one in Europe. The trials, which were supported by funding from NCI's Small Business Innovation Research (SBIR) program and venture capital, were completed in 2014 and validated that this test could determine the likelihood that lung nodules were either benign or malignant.

The company was acquired the following year by Veracyte, a publicly traded genomic diagnostics company, which launched the test commercially as Percepta®. In 2017, Medicare began covering Percepta® as a diagnostic tool to expand the use of bronchoscopy in detecting lung cancer.

"It's gratifying to see something that started at the bench make it all the way to a patient," Avrum reflected, "but it was a long journey—more than 10 years." Acknowledging NCI's involvement both in the basic research and commercialization, he said, "Percepta® is now a product because of NCI's support." Striving to develop even better technology, he has found, with funding from NCI's Early Detection Research Network, that some of the same molecular damage seen in the upper airway is also present in the nose, which would enable even easier and less-invasive testing.

TREATING CANCER

NCI's commitment to developing new treatments for cancer patients spans basic research to discover the mechanisms of cancer, preclinical research to investigate the anticancer effects of therapies that target these mechanisms, and clinical research to test new therapies in patients. Despite recent advances in targeted therapy and immunotherapy, more needs to be done to substantially improve the outlook for both adults and children with cancer. Three areas for further investment include developing combination therapies, biomarker-guided immunotherapies, and precision medicines that target specific abnormalities in a patient's cancer.

Combining Therapies to Improve Outcomes

Combination therapies have proven to be vitally important in the successful treatment of patients with many types of cancer. Combining treatments that have different mechanisms of action can kill more cancer cells and reduce the chance that drug resistance will emerge. The overall goal is to improve a patient's response to therapy without substantially increasing toxicity.

In recent years, the identification of new combination therapies has accelerated, with hundreds of clinical trials testing combinations that include chemotherapy drugs, radiation therapy, hormonal therapies, molecularly targeted therapies, and immunotherapies. However, a more systematic approach is needed to identify the most promising combinations among the many thousands of possibilities, advance them to clinical trials, and make them available to patients who will benefit from them.

NCI plays an important role in supporting the research needed to develop combination therapy approaches. In addition, NCI brings different institutions and organizations together to advance this area of research. Examples of Food and Drug Administration (FDA)-approved drug combinations that have been studied in NCI-sponsored clinical trials are docetaxel (Taxotere®), doxorubicin, and cyclophosphamide for breast cancer and oxaliplatin (Eloxatin®), 5-fluorouracil, and leucovorin (Wellcovorin®) for colorectal cancer.

THE VISION

To identify the combination therapies that will be most effective for each patient

THE APPROACH

- Support research to identify therapies that, when combined, will work better than they would alone
- Systematically evaluate treatment combinations in preclinical studies
- Evaluate the most promising treatment combinations in clinical trials

Research Priorities

NCI advances combination therapies for cancer by supporting preclinical research and testing promising combinations in clinical trials.

Support Basic and Preclinical Research to Identify Combination Therapies

Research should guide the selection of candidate combination treatments. This research can provide deeper insights into the mechanism(s) of action of individual treatments, how different treatments might work together, the potential side effects that may occur when treatments are combined, and how new combinations might be given to patients (doses and schedule).

NCI efforts include several resources for researchers:

- To aid in the systematic development of combination therapies, NCI's Developmental Therapeutics Program created the **NCI ALMANAC**, a public resource that contains data on more than 5,000 pairs of FDA-approved drugs that were screened at different doses against 60 human cancer cell lines (the NCI-60 Human Tumor Cell Lines Screen). In one study, NCI researchers tested two drug pairs in the NCI ALMANAC that exhibited potent cell-killing activity. Nilotinib (Tasigna®) plus paclitaxel (Taxol®) and bortezomib (Velcade®) plus clofarabine (Clolar®) had antitumor activity in several mouse models of human cancer. The results of these studies were convincing enough that both combinations are being tested in early-phase clinical trials.

- **Models of human cancer** help researchers screen drug combinations for effectiveness and study ways to overcome the problem of drug resistance. NCI facilitates the development of new models of human cancer, including new tumor cell lines and mice bearing patient-derived tumor grafts (known as patient-derived xenografts, or PDXs). Some models are available upon request to researchers in the United States through the NCI Patient-Derived Models Repository.

Facilitate Clinical Trials of Promising Treatment Combinations

NCI leads several initiatives to investigate promising combination therapies in clinical trials, including funding for investigator-initiated trials and resources for researchers.

- **NCI has funded more combination therapy studies than any other organization.** Stories about several of these trials are highlighted in this section, including the story of trial participant and ovarian cancer survivor Betsy Brauser of Florida (page 42); Valerie Winston of Maryland, who participated in a trial for high-risk smoldering myeloma (page 43); and a research team at the University of Pennsylvania, who combined radiation therapy with immune checkpoint blockade (page 44).

- To facilitate testing of new drug combinations by academic investigators, NCI launched the **NCI Formulary** in 2017. The formulary is a public–private partnership between NCI and pharmaceutical and biotechnology companies that gives investigators at NCI-Designated Cancer Centers rapid access to agents or combinations of agents, from multiple pharmaceutical companies, for preclinical testing and clinical trials. The formulary is designed to drastically shorten the amount of time needed to obtain treatments from more than one company.

- A major activity of NCI's Cancer Therapy Evaluation Program is oversight of the **National Clinical Trials Network (NCTN)**, which can facilitate combination therapy trials. NCTN is one of the largest publicly funded cancer trials organizations in the world and provides the infrastructure and streamlined mechanisms to plan and conduct cancer clinical trials efficiently throughout the United States. NCTN facilitates proposal submission, timely review by the collaborating pharmaceutical companies, agent distribution, serious adverse event reporting, and clinical data reporting, while providing a coordination mechanism between the clinical investigators and the pharmaceutical company collaborators.

KEY TAKEAWAYS

- NCI is committed to developing new combination therapies that will extend the lives of more cancer patients.
- NCI supports the development of new models of human cancer, including in racial/ethnic populations, to advance the testing of combination therapies and find ways to overcome the problem of drug resistance.
- NCI is uniquely positioned to bring together different institutions, organizations, and companies to advance this area of research.

BETSY BRAUSER

Ovarian Cancer Survivor
Florida

COMBINING DRUGS TO TREAT OVARIAN CANCER

Betsy Brauser was diagnosed with stage IIC ovarian cancer in 2009. She underwent standard platinum-based chemotherapy, and her doctors gave her an all-clear. But a year later, scans revealed her cancer had returned. So, she found a phase I clinical trial for patients with ovarian cancer at the NCI-Designated Dana-Farber/ Harvard Cancer Center in Massachusetts.

Ovarian cancer is the fifth leading cause of cancer death among women in the United States. "Approximately 70% of the women diagnosed with ovarian cancer will die from the disease," explained Joyce Liu, M.D., a principal investigator of the trial. "It's critical that we find more effective and better tolerated treatments to help women live better and live longer," she said.

So, Joyce and her colleagues at Dana-Farber designed a trial combining the Food and Drug Administration-approved drug olaparib (Lynparza™) with the investigational drug cediranib. Olaparib inhibits an enzyme called PARP, and cediranbib inhibits the growth of blood vessels that tumors need to grow larger than about 1 mm in size.

Joyce received support from NCI in 2008, when she began developing the phase I trial, her first investigator-initiated trial as an early-career researcher. She drew on several NCI-funded preclinical studies that indicated these drugs might work much better together than either worked alone. "It's an exciting possibility that we might make a tumor more vulnerable to a drug by adding a different class of drugs," she reflected. "That's the power of combination—having a true synergistic effect."

Betsy enrolled in Joyce's trial and spent the next several years commuting to Boston for treatment. Scans taken at 3- to 4-month intervals showed her tumors were shrinking, and, eventually, her doctors reported that they found no evidence of disease. Betsy and her family were elated.

Betsy continues to receive follow-up checks on the trial, which has moved successfully from a phase I and then phase II trial into an NCI-sponsored phase III trial to determine whether the combination regimen is more effective than olaparib or chemotherapy alone. She hopes that scientists continue conducting research and developing drugs to help other patients with ovarian cancer.

Joyce agrees: "We need to understand what drives ovarian cancer at a biological level and find new ways to overcome resistance to platinum-based drugs. Combinations of therapies that build on our understanding of the various types of ovarian cancer will go a long way toward helping doctors better treat their patients."

STOPPING MULTIPLE MYELOMA IN ITS TRACKS

VALERIE WINSTON

Smoldering Myeloma Survivor
Maryland

Valerie Winston is thankful that she went to her doctor for a routine physical examination in 2009. The results of standard tests indicated that she was at risk for multiple myeloma. Thanks to a clinical trial testing a combination of therapies for individuals like Valerie, she never had to experience cancer's full impact.

Multiple myeloma will be diagnosed in approximately 30,280 Americans in 2017, and an estimated 12,590 of them will die from it. Multiple myeloma is a cancer of plasma cells—cells in the immune system that help the body fight infection. Abnormal plasma cells make proteins called M proteins, which are abnormal antibodies that build up in the bone marrow and can damage the body. An M protein is what Valerie's doctors detected.

Because Valerie had low levels of the M protein and no other symptoms of cancer, she was diagnosed with a condition called monoclonal gammopathy of undetermined significance (MGUS). MGUS is not cancer, but, in some cases, MGUS can progress to multiple myeloma. Valerie's initial elation that the condition had been caught early dimmed when her doctors told her that they would need to "watch and wait" to see if cancer developed before they could treat her.

Valerie was monitored, and, eventually, she progressed to a disease called smoldering myeloma, which is a stage between MGUS and multiple myeloma where myeloma cells are present but not causing bone or organ damage. Now, she was deemed at high risk for progression to full-blown multiple myeloma.

Because more than 90% of patients with high-risk smoldering myeloma develop multiple myeloma within 2–5 years, researchers are working to intervene in this process. One way is by testing drugs against high-risk smoldering myeloma that have been successful against multiple myeloma. Impatient to do something beyond "watching and waiting," Valerie found a clinical trial at NCI. "I went into the trial with the attitude that, if it doesn't help me, then my participation will help someone else in the future," she said.

The trial Valerie participated in tested lenalidomide (Revlimid®), dexamethasone, and carfilzomib (Kyprolis®), three drugs that are already approved by the Food and Drug Administration to treat multiple myeloma. Researchers wanted to see if the combination of these drugs would provide a safe and effective treatment for patients with high-risk smoldering myeloma.

Valerie began showing good results by the 3rd month of treatment, and, by the 9th month, doctors proclaimed she had experienced a complete response. In fact, all 18 patients in the trial responded to the treatment. Although it was a small study, these results provide evidence to support larger trials in the future that will determine more definitively whether the benefits of this experimental treatment outweigh the harms.

Despite having some side effects from treatment, Valerie is grateful to have participated in the trial. She is now a messenger about the importance of research to family, friends, and anyone who will listen. "I talk to my relatives and others about this," she said. "We all have a part to do. I feel great about being part of this progress."

JOINING FORCES AGAINST CANCER

ROBERT (BOB) VONDERHEIDE, M.D., D.PHIL.

Director, Abramson Cancer Center, University of Pennsylvania

ANDY MINN, M.D., PH.D.

Associate Professor of Radiation Oncology, University of Pennsylvania

CHRISTINA TWYMAN-SAINT VICTOR, M.D.

Assistant Professor of Medicine, University of Pennsylvania

A cross-disciplinary team of scientists and physicians at the University of Pennsylvania is redefining the role of one of cancer medicine's oldest tools and blazing a new trail in the treatment of patients. Their efforts, led by cancer immunologist and oncologist Bob Vonderheide and radiation oncologist Andy Minn, are demonstrating the promise of combining immune checkpoint inhibitors and radiation therapy.

Radiation therapy has been used to treat patients with cancer since the beginning of the 20th century. About half of all cancer patients receive some type of radiation therapy. It is typically used as a local therapy—that is, to treat the specific area of the body where a tumor is located. However, mounting evidence supports the idea that local radiation can also have effects throughout the body and that these effects are mediated by the immune system.

In fact, researchers are finding that as irradiated cancer cells die, they trigger an immune response much like vaccines do. Bob, Andy, and their colleagues—calling themselves the RadVax team (Rad for radiation and Vax for vaccine)—are testing the idea that the immune response triggered by radiation can be improved further by the addition of immune checkpoint inhibitors, a type of treatment that enhances the ability of the immune system to kill a tumor. If successful, the combination therapy will provide additional options for patients with metastatic cancer, including patients who do not respond to checkpoint inhibitors alone.

In 2015, the team reported results from the first clinical trial of radiation therapy combined with the immune checkpoint inhibitor ipilimumab (Yervoy®), which targets a protein called CTLA-4. In addition to testing the combination in patients with metastatic melanoma, they also studied it in mouse models of melanoma to gain further biological insights.

Although responses were observed in some of the patients, most did not benefit. However, studying both the mice and patient samples uncovered a resistance mechanism—a way in which the melanoma cells avoided being killed by the immune system—that likely explained the clinical findings. This led the team to their current strategy of deploying multiple checkpoint antibodies along with radiation. The triple combination, effective in mice, is currently being tested in patients in clinical trials.

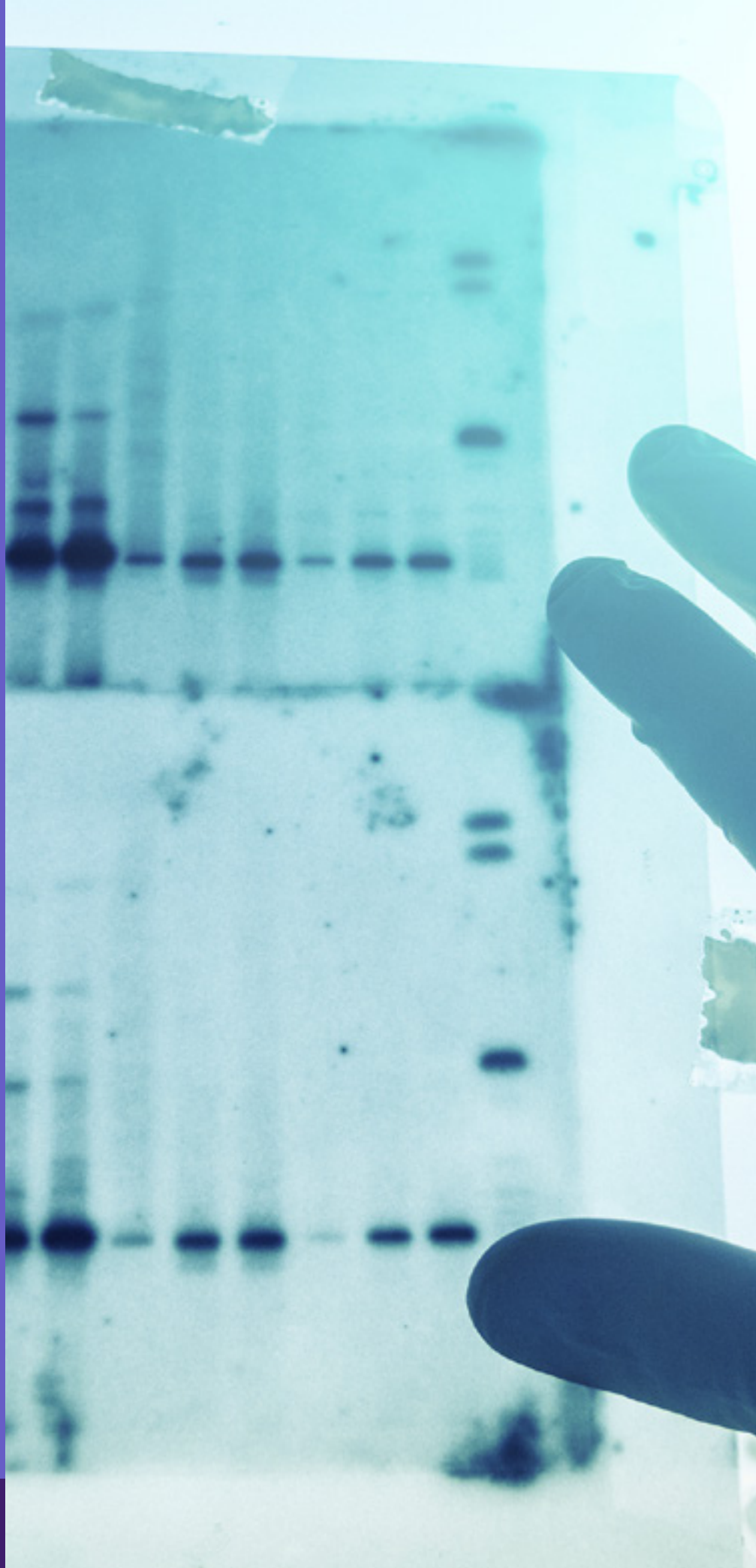
Bob credits the NCI Cancer Center Support Grant (CCSG) to Abramson Cancer Center for the team's success. Access to the infrastructure and personnel supported by the CCSG enabled the researchers to be nimble and get the studies off the ground quickly. This was a "CCSG in action," said Bob.

The team that accomplished this study consisted of 25 researchers from a

variety of scientific disciplines and included early-career and established investigators. Notably, the study's first author Christina Twyman-Saint Victor was completing her research training at the time and is now an independent investigator with her own laboratory at Penn.

Additional clinical trials testing combinations of radiation therapy and immune checkpoint inhibitors are currently being conducted. Still, "there are many scientific questions that still need to be answered," said Andy. With NCI's support, the RadVax team aims to answer them. For example, more needs to be known about how these treatments interact at the cellular and molecular level to inform how best to combine them.

In 2017, NCI awarded Bob and Andy, along with Professor of Radiation Oncology Amit Maity, M.D., Ph.D., and Distinguished Professor of Microbiology E. John Wherry, Ph.D., a grant to continue this work in four cancer types. "Our team has one goal: to improve the health of patients," said Bob. "We are using science to do that."



Developing Precision Immunotherapies

Immunotherapy is a type of treatment that helps the body's immune system fight cancer. Several kinds of immunotherapy, including immune checkpoint inhibitors, adoptive cell transfer, and therapeutic vaccines are either commercially available or in clinical development. To date, six immune checkpoint inhibitors have been approved by FDA for the treatment of eight types of cancer.

One of the inhibitors has also been approved to treat any solid tumor that has a specific genetic feature. This was the first FDA approval of its kind and a major advance for precision cancer medicine, in which the molecular characteristics of a tumor are used to identify effective therapies. (Read more about this drug approval on page 52.)

Recent advances in cancer immunotherapy are the result of several decades of basic research, much of it supported by NCI, on the function of the immune system and how it can be used for the treatment of cancer.

FDA-Approved Immune Checkpoint Inhibitors

Inhibitor	Target	Cancer Type(s)
Atezolizumab (Tecentriq®)	PD-L1	Bladder cancer Non-small cell lung cancer
Avelumab (Bavencio®)	PD-L1	Bladder cancer Merkel cell carcinoma*
Durvalumab (Imfinzi™)	PD-L1	Bladder cancer
Ipilimumab (Yervoy®)	CTLA-4	Melanoma*
Nivolumab (Opdivo®)	PD-1	Bladder cancer Head and neck cancer (squamous cell carcinoma) Classical Hodgkin lymphoma Melanoma Mismatch repair deficient and microsatellite instability-high colorectal cancer* Non-small cell lung cancer Renal cell (kidney) cancer
Pembrolizumab (Keytruda®)	PD-1	Bladder cancer Head and neck cancer (squamous cell carcinoma) Classical Hodgkin lymphoma† Melanoma Mismatch repair deficient and microsatellite instability-high solid tumors† Non-small cell lung cancer

*patients age 12 and older
†pediatric and adult patients

Despite the remarkable progress made to date in cancer immunotherapy, most patients do not benefit from currently available treatments, and these therapies can be toxic to some individuals. Understanding why these treatments are not beneficial for more patients is a pressing question for scientists. However, NCI-funded research has led to the identification of two biomarkers that can help determine which patients are more likely to respond to checkpoint inhibitor therapy: PD-L1 and a genetic feature called microsatellite status. Patients whose cancers have these biomarkers are more likely to respond to checkpoint inhibition than patients whose cancers do not. (Read about why more biomarkers are needed for patients in the story about melanoma survivor T.J. Sharpe of Florida on page 50.)

NCI supports a wide range of research, from basic research to clinical trials, to advance the field of cancer immunotherapy. Through this work, the benefits of immunotherapy will be extended to more patients with cancer.

THE VISION

To develop safe and effective immunotherapy options for all patients with cancer

THE APPROACH

- Advance research on the mechanisms of immunotherapy response, resistance, and toxicity
- Support research, infrastructure development, and collaboration to discover and validate clinically useful immunotherapy biomarkers

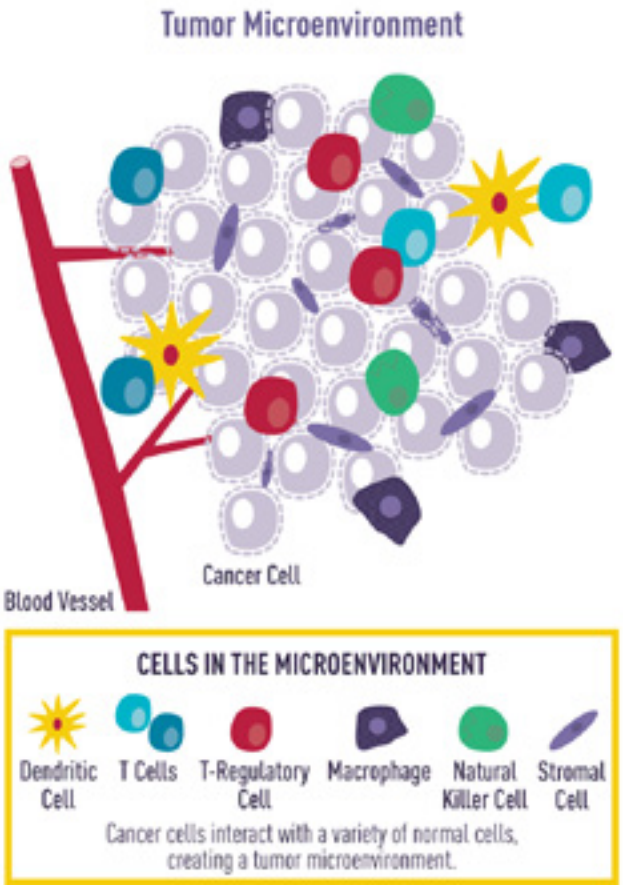
Research Priorities

Additional basic research, translational studies, and clinical trials are critical for further elucidating the mechanisms of immunotherapy response, resistance, and toxicity and for identifying additional biomarkers to guide treatment selection.

Advance Research on Mechanisms of Immunotherapy Response, Resistance, and Toxicity

The effectiveness of immunotherapy in patients is influenced by several factors, including interactions between cancer cells, immune cells, and stromal (connective tissue) cells in the tumor microenvironment and the characteristics of the cancer cells themselves. Research is leading to key discoveries about these factors, but more work is needed to increase this knowledge and translate it into safer and more-effective immunotherapy options for patients. This ongoing research includes studies of:

- **The tumor microenvironment**: To eradicate cancer cells, immune cells (white blood cells) must travel to the site of the



tumor and infiltrate it. However, some tumors, including pancreatic and prostate tumors, can exclude immune cells from their microenvironment, making then unresponsive to immunotherapy. These tumors are called "noninflamed" or "cold" tumors. In contrast, "inflamed" or "hot" tumors, such as melanoma, contain immune cells in the tumor microenvironment and, therefore, tend to respond better to immunotherapy. How noninflamed tumors exclude immune cells and whether they can be turned into inflamed tumors are major unanswered questions that NCI-supported research is addressing.

- **Immune cells**: Although a particular type of white blood cell is directly responsible for killing tumor cells, many other types of immune cells are involved in either promoting or suppressing immune responses against cancer. Scientists aim to better understand how these different cells interact with one another. As an example, NCI-funded researchers discovered that breast cancer cells and immune cells called macrophages "talk" by secreting factors that support tumor growth and invasiveness. The cancer cells secrete a protein called colony stimulating factor 1 (CSF-1) that stimulates the macrophages to produce a protein called epidermal growth factor (EGF). The EGF, in turn, promotes further cancer cell production of CSF-1, thereby generating a positive feedback loop.

- **Cancer cells**: Research funded by NCI and led by Suzanne Topalian, M.D., and her colleagues at Johns Hopkins University demonstrated that tumors with high levels of the protein PD-L1 tend to respond better to PD-1 inhibitors. PD-L1 binds to the PD-1 protein on immune cells, suppressing an immune response. This finding and additional research by others led to FDA-approved tests that measure PD-L1 expression on patients' tumors—making PD-L1 the first approved biomarker to guide the use of cancer immunotherapy. In another area of research, NCI-funded scientists have identified specific gene mutations and patterns of gene expression in certain cancer types that indicate responsiveness or resistance to PD-1 inhibitors.

Support Collaboration and Data Sharing to Discover and Validate Immunotherapy Biomarkers

Sharing samples and data through research and clinical trial networks will help advance research in cancer immunotherapy. There are several NCI-supported efforts that will help facilitate this sharing.

- The **Cancer Immunotherapy Trials Network (CITN)**, which was established in 2010 to design, facilitate, and conduct early-phase immunotherapy clinical trials and support research on patient tumor specimens. The network currently has 30 participating trial sites and has conducted 10 clinical trials to date. CITN works with academic, industry, and nonprofit partners to advance promising immunotherapies to the clinic more efficiently and cost effectively. For example, the network led a phase II clinical trial that demonstrated the effectiveness of the checkpoint inhibitor pembrolizumab in patients with Merkel cell carcinoma, a rare but aggressive form of skin cancer.

- Other NCI clinical trial networks, including the **Experimental Therapeutics Clinical Trials Network** and the **National Clinical Trials Network**, which provide infrastructure, funding, and sponsorship for immunotherapy and other treatment trials. Since 2010, more than 90 phase I to phase III trials have been initiated in NCI networks for immunotherapy agents and novel combinations involving immunotherapy. Most trials incorporate research on biomarkers and other studies to better understand why these therapies work for some patients and not others.

- In 2017, NCI announced the formation of a new network of laboratories that will be responsible for the comprehensive molecular analysis of clinical trial specimens for biomarkers associated with response to immunotherapy. The **Cancer Immune Monitoring and Analysis Centers (CIMACs)** will conduct correlative studies and profiling of tumors and immune cells for NCI-funded early trials of immunotherapy. Part of this effort includes the creation of a **Cancer Immunologic Data Commons (CIDC)** to support the bioinformatics needs of the CIMACs. The database created by the CIDC will serve as a resource for the identification of novel biomarkers and targets for patient selection and treatment, as has been done with NCI's Genomic Data Commons for genomic data.

- As part of the Cancer Moonshot[SM], NCI is establishing two networks to accelerate the translation of immunotherapy research discoveries to clinical applications for adult and pediatric cancers. For adult cancers, the **Immuno-Oncology Translational Network** aims to improve outcomes for patients who are treated with immunotherapy and to prevent cancers before they can occur through immunoprevention approaches. The **Pediatric Immunotherapy Discovery and Development Network** will identify new targets for immunotherapies, developing new pediatric immunotherapy treatment approaches, and defining the biological mechanisms by which pediatric tumors evade the immune system.

KEY TAKEAWAYS

- NCI supports research to develop safe and effective immunotherapy options for all cancer patients.
- NCI funds research to determine the mechanisms of immunotherapy response, resistance, and toxicity to aid in the discovery of biomarkers that will be useful in guiding clinical decision making.
- NCI facilitates sharing samples and data through research and clinical trial networks that advance research in cancer immunotherapy.

T.J. SHARPE

Melanoma Survivor
Florida

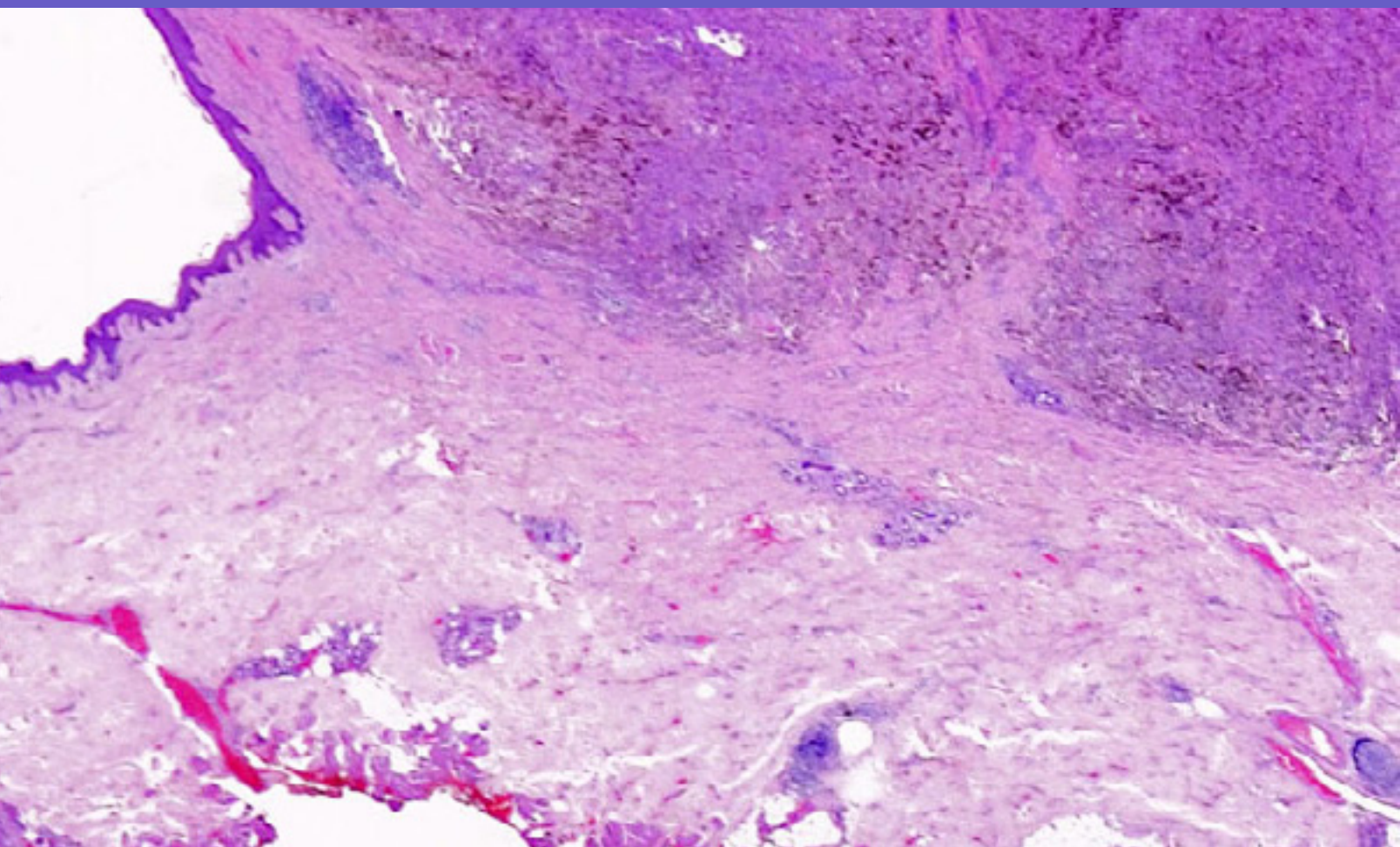
MAKING THE CASE FOR BIOMARKERS

In August 2012, just weeks after the birth of his second child, 37-year-old T.J. Sharpe walked into his local emergency room with a spiking fever and did not leave for more than 2 weeks. He was blindsided by the diagnosis he received: metastatic melanoma. Twelve years earlier, a stage IB melanoma had been removed from his chest. T.J. had been careful about his sun exposure ever since. But now, melanoma tumors riddled his lungs, liver, spleen, and small intestine.

T.J.'s first oncologist recommended chemotherapy and expressed doubt that he would be alive in 2 years. T.J. and his wife, Jen, deciding that was not acceptable, sought additional medical opinions and, ultimately settled on a clinical trial that was testing a combination of immunotherapies that had not previously been given to patients. T.J. did not benefit from this trial. "I was the first to try that combination, and I was the first to fail it," he said. The regimen was arduous, and he experienced many complications.

Despite this setback, he enrolled in another trial. "I knew that clinical research was far from a guarantee but held the promise of hope," he said. "My children, Josie and Tommy, were growing up right in front of me, and I was willing to endure anything." Within a matter of weeks of receiving his first dose of the drug being tested in the new trial—a PD-1 checkpoint inhibitor—his tumors shrank by half. Five years later, T.J. remains cancer free.

Based on the success of this and many other clinical trials, the Food and Drug Administration (FDA) has approved five PD-1/PD-L1 checkpoint inhibitors to treat



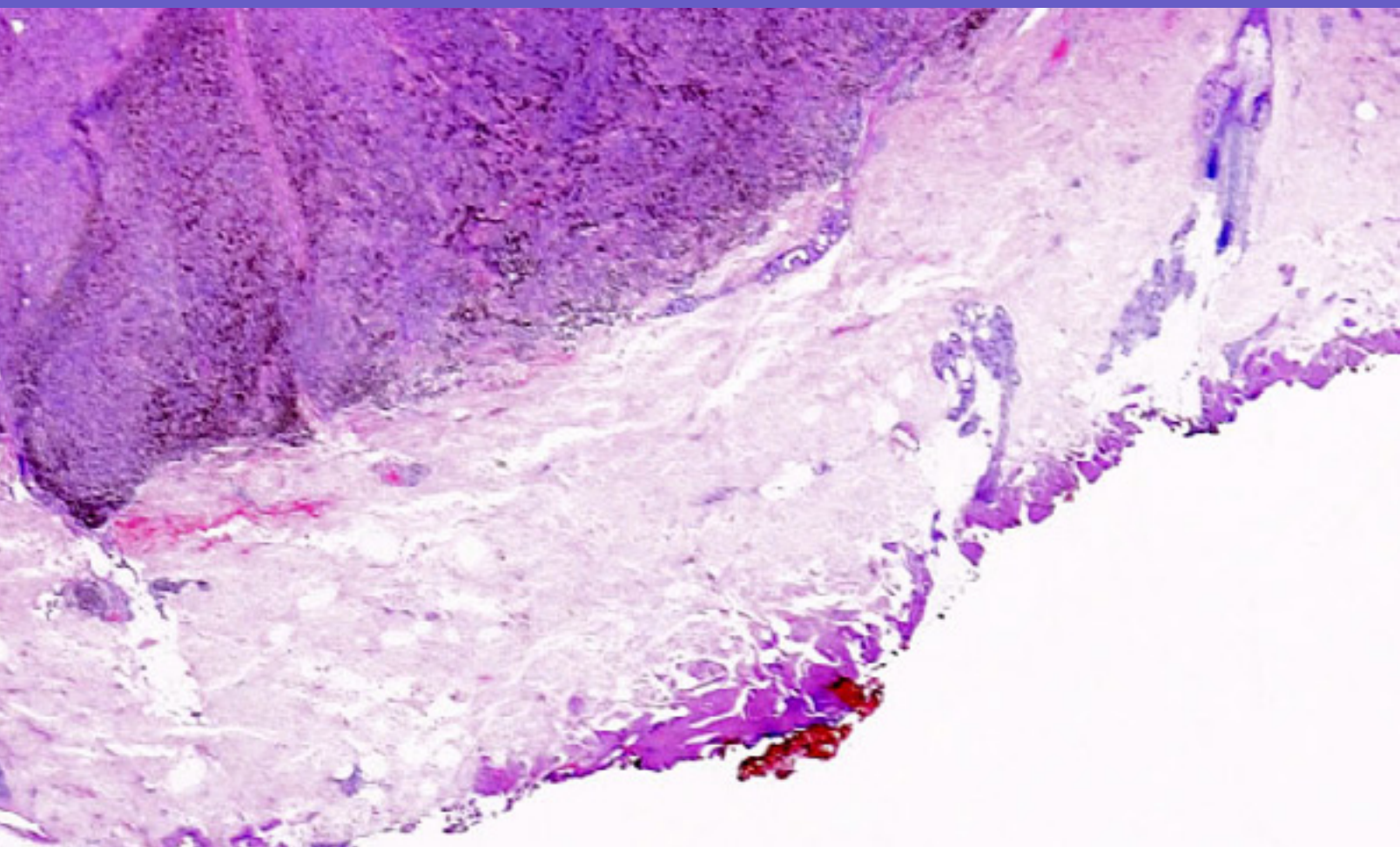
melanoma and other cancers since 2014.

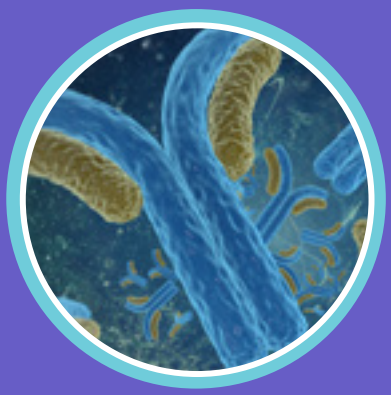
NCI supported the initial work necessary to unleash the immune system against cancer with studies of ipilimumab (Yervoy®), the first immune checkpoint inhibitor to be approved by FDA. Ipilimumab blocks an immune checkpoint protein called CTLA-4. NCI-funded research had shown that blocking CTLA-4 improved the ability of the immune system to attack cancer in animal models. This pioneering work formed the basis of ipilimumab's approval for patients with metastatic melanoma in 2011 and paved the way for future immunotherapies like the one that T.J. received.

Long-term follow-up of melanoma patients treated with ipilimumab in clinical trials have demonstrated that approximately 20% of patients were still alive 10 years later. Follow-up data from trials of approved PD-1 inhibitors show that approximately one-third of patients were alive at least 5 years after treatment with nivolumab (Opdivo®), and 40% of patients were alive 3 years after treatment with pembrolizumab (Keytruda®).

For a disease as deadly as metastatic melanoma, this is great progress. Yet, this also means that most patients do not experience a long-lasting benefit from the drugs. "Without further research, we will never know why I am living and so many others have not benefited," said T.J., reflecting on the need for biomarkers to help doctors identify the best treatment for each cancer patient. Several factors influence the effectiveness of immunotherapy in patients. NCI is supporting ongoing work to identify biomarkers of immunotherapy response, resistance, and toxicity.

It has been 5 years since T.J.'s diagnosis with metastatic melanoma. His aspirations for the next 5 years include watching his son turn 10. "He was just weeks old when my melanoma came back. Every birthday for him is a small milestone for me, too." Through this journey, T.J. became a blogger and advocate aiming to make a difference in the lives of other patients. "If, for some reason, I am not around in 5 years, I also hope those years are filled with impact so that other patients and families have the most valuable medicine of all—hope."





DEVELOPING THE FIRST PRECISION MEDICINE

In May 2017, the Food and Drug Administration (FDA) approved the first drug to treat tumors based on their genetic characteristics, regardless of where in the body the cancer originated. Until now, drugs have been approved based on their cell or tissue of origin, such as the breast or the lung. But pembrolizumab (Keytruda®) doesn't target the genetic abnormalities of cancer cells specifically—it targets the immune system.

How did pembrolizumab become the first FDA-approved "tumor-agnostic" precision medicine drug? This historic accomplishment was enabled by more than three decades of NCI-funded research in cancer genetics and immunology. The drug is now available for patients with late-stage solid tumors with a genetic feature called microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). Whereas precision medicine has focused largely on developing and testing drugs that target the genetic abnormalities that drive cancer cell growth, this new precision medicine approach uses the genetic information in tumors as a biomarker, not a target, to identify patients who may benefit from treatment with pembrolizumab.

When the cells of the body divide, their DNA must be copied so each progeny cell receives a full complement. This process, known as DNA replication, is not always perfect and mistakes can be made. Normally, however, cells have ways of repairing these mistakes. In cells with dMMR, genes responsible for a DNA repair process known as mismatch repair are mutated. This DNA repair defect can be inherited (as it is in a condition called Lynch syndrome), or the defect can happen by chance (sporadically). The failure of cells with dMMR to repair mistakes made in DNA replication leads to the accumulation of hundreds to

thousands of mutations, some of which can cause cancer.

Lynch syndrome is named after NCI-funded researcher Henry T. Lynch, M.D., who discovered the syndrome in the early 1970s by studying affected families that demonstrated an increased risk of colorectal and several other types of cancer. In the 1990s, several NCI-funded research teams investigating the genetics of hereditary colorectal cancer determined that mutations in mismatch repair genes play a key role in this syndrome. Two of these teams were led by Richard Kolodner, Ph.D., of the Ludwig Institute for Cancer Research, and Bert Vogelstein, M.D., of Johns Hopkins University.

In addition to hereditary and sporadic colorectal cancers, dMMR is associated with some cancers of the uterus, ovary, prostate, stomach, small intestine, biliary tract, and pancreas.

Scientists have found that cancers with many mutations, such as lung cancer and melanoma, are more likely to respond to pembrolizumab and other immunotherapy drugs than cancers with low numbers of mutations. Researchers hypothesized that tumors with dMMR—because of their high number of mutations—might also respond to these drugs, including pembrolizumab.

One trial, led by Johns Hopkins researcher Dung Thi Le, M.D., was funded in part by several NCI grants, including a Cancer Center Support Grant and a Specialized Program of Research Excellence Award. Forty-one patients were enrolled in this trial, 32 of whom had colorectal cancer. Forty percent of patients with dMMR colorectal cancer responded to treatment, compared with 0% in patients without the defect.

These results and other data led FDA to grant pembrolizumab accelerated approval for the treatment of dMMR cancers. This approval is significant because targeting genetic characteristics, rather than where the cancer originates in the body, opens up new options for patients who might otherwise not be considered candidates for a drug. Furthermore, this example demonstrates that decades of NCI-funded research in different areas, including cancer genetics and immunology, has resulted in a whole greater than the sum of its parts for patients.

Developing New Treatments for Children with Cancer

Cancer is the leading cause of death from disease among children and adolescents in the United States, with approximately 15,000 new cases and 2,000 deaths among those ages 19 and younger each year. Fifty years ago, many childhood cancers were virtually incurable. However, NCI's investments in research have led to effective treatments for several types of pediatric cancer, including acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma. Today, the 5-year overall survival rate for childhood cancer has increased to more than 80%, together with substantial decreases in overall mortality for children with cancer.

Nevertheless, progress against all cancers that affect children and adolescents is urgently needed, especially against those for which effective treatments do not currently exist, such as diffuse intrinsic pontine glioma (DIPG) and malignant rhabdoid tumor.

Treatment regimens for children and adolescents with cancer are often associated with substantial short-term toxic side effects. In addition, childhood cancer treatments may cause serious health problems for survivors months or years later, including higher risks of heart disease, stroke, infertility, and second cancers. More research is needed to understand these adverse side effects of treatment and how to prevent or mitigate them.

The rarity of childhood cancers—less than 1% of all cancers diagnosed in the United States each year—makes them difficult to study and discourages pharmaceutical companies from developing treatments. Consequently, NCI's leadership and funding are critically important for continued progress against childhood cancers.

THE VISION

To have safe and effective therapies for every type of childhood cancer

THE APPROACH

- Support research to develop more-effective, less-toxic treatments for pediatric cancers, including molecularly targeted therapies and immunotherapies, and test them in clinical trials
- Improve the long-term quality of life of survivors of childhood cancer
- Facilitate greater collaboration among investigators dedicated to childhood cancer research

Research Priorities

NCI supports research ranging from the biology of childhood cancer to clinical trials that test new cancer treatments in children and adolescents in clinical trials. Two areas of focus are molecularly targeted therapies and immunotherapies.

Support the Development of Targeted Therapies for Childhood Cancers

Cancers that arise in children and adolescents often differ from those that arise in

adults. For example, they generally have fewer genomic alterations than adult cancers. To address this, NCI supports several initiatives to identify the genomic changes that drive childhood cancers, develop new treatments to target those changes, and test the treatments in precision medicine clinical trials.

- The **NCI–Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice (NCI–COG Pediatric MATCH)** trial aligns with the Precision Medicine Initiative® in oncology. Launched in 2017, this trial will determine whether treating cancers based on their molecular abnormalities, rather than the type of cancer, can be effective. The trial design was based on the NCI-MATCH trial for adult cancers. NCI–COG Pediatric MATCH is open to children and adolescents who have advanced solid tumors that have progressed on standard treatment or for which no agreed upon standard treatment exists. The trial will enroll patients whose tumors have a molecular abnormality that is targeted by one of the approved or investigational therapies that are being used in the trial.

- The **Therapeutically Applicable Research to Generate Effective Treatments (TARGET)** initiative has supported a consortium of scientists who are conducting comprehensive molecular analyses to identify the genomic changes that drive several hard-to-treat childhood cancers. The genomic profiling of pediatric acute myeloid leukemia (AML) at initial diagnosis, remission (after treatment), and relapse (recurrence) was recently accomplished because of this initiative. This profiling confirmed that the genomic features of pediatric AML differ from those in adult AML and provided important information to guide future drug development and clinical management of the disease.

- The **Pediatric Preclinical Testing Consortium** is testing cancer drugs in preclinical models of pediatric cancers to help prioritize which agents to pursue in human clinical trials. The consortium includes NCI and five academic research institutions. Albert Einstein College of Medicine is studying models of osteosarcoma; Greehey Children's Cancer Research Institute is studying sarcoma and kidney cancers; Baylor College of Medicine is studying brain cancers; Children's Hospital of Philadelphia is studying neuroblastoma; and Australia's Children's Cancer Institute is studying leukemia.

- Childhood cancers are often driven by so-called **fusion oncogenes**, which are formed when parts of two different genes become joined to one another. To date, few treatments have been developed that target the abnormal proteins, or fusion oncoproteins, produced by these genes. Developing therapies against pediatric fusion oncoproteins is a high priority and an effort that will be accelerated through the Cancer Moonshot.

- **DIPG**, a type of malignant brain stem tumor, is perhaps one of the most devastating cancers diagnosed in children. Most patients die within 2 years of diagnosis. However, NCI-funded researchers at St. Jude Children's Research Hospital and the Washington University School of Medicine have recently discovered a specific mutation in DIPG tumors that is thought to drive their growth. The mutation affects a cell's ability to normally modify a protein, called histone 3.3, in chromosomes as

NCI-Children's Oncology Group Pediatric MATCH Trial*

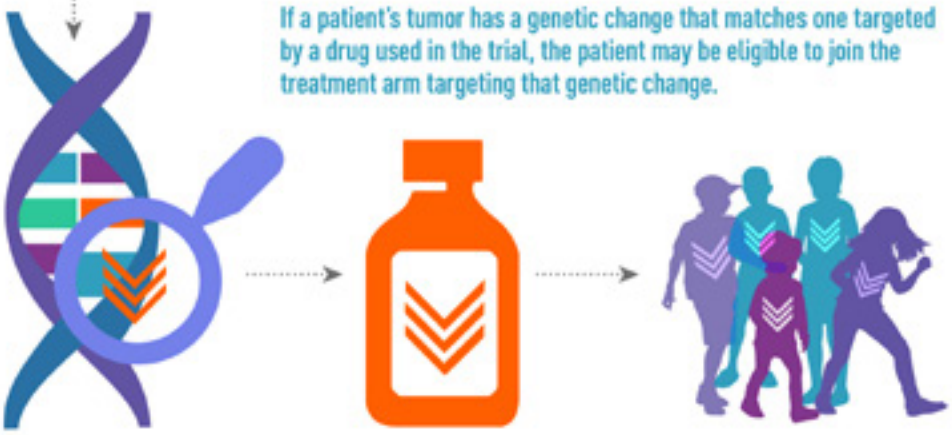
This precision medicine clinical trial, funded by NCI and conducted by COG, matches children and adolescents with treatment based on genetic changes in their tumors.

Pediatric MATCH is for patients ages 1 to 21 who have both:

- Solid tumors, including lymphomas and brain tumors, or histiocytoses
- Tumors that no longer respond to standard treatment or that have come back after treatment

ABOUT 200-300 PEDIATRIC PATIENTS ARE EXPECTED TO BE SCREENED EACH YEAR

TUMOR TISSUE WILL UNDERGO TESTING FOR CHANGES IN MORE THAN 160 GENES



If a patient's tumor has a genetic change that matches one targeted by a drug used in the trial, the patient may be eligible to join the treatment arm targeting that genetic change.

Talk with your pediatric oncologist about whether this trial would be an option for your child.

THE TRIAL IS OFFERED IN THE U.S. AT ABOUT —200— CHILDREN'S ONCOLOGY GROUP SITES

Call NCI's Contact Center (formerly known as the Cancer Information Service) to learn more about the trial or trial locations at 1-800-4-CANCER (1-800-422-6237) for assistance in English and Spanish.

*The Pediatric Molecular Analysis for Therapy Choice (MATCH) trial is being led jointly by NCI and the Children's Oncology Group (COG), part of the NCI-sponsored National Clinical Trials Network (NCTN).

a means of controlling gene expression. This finding has led to a clinical trial of the drug panobinostat (Farydak®) in children with DIPG. The trial is being conducted through the **Pediatric Brain Tumor Consortium** at ten sites across the country, including NCI's Pediatric Oncology Branch at the NIH Clinical Center. Formed by NCI, the consortium facilitates multicenter studies, research, and data sharing to improve treatment strategies for children with brain cancers.

- NCI intramural researchers are leading the development of a new targeted therapy approach for children with **rare tumors**, such as neurofibroma tumors, a disease in which tumors form in nerve tissue and for which there are no FDA-approved drugs. (Read more about this research in the story about Philip Moss of Alabama on page 59.)

Advance Immunotherapies for the Treatment of Children with Cancer

Despite the remarkable progress made in immunotherapy against adult cancers, some immunotherapy approaches have yet to be evaluated for the treatment of childhood cancers. With this in mind, NCI will fund research aimed at advancing more immunotherapies for childhood cancers to the clinic.

- Major progress in treating childhood acute lymphoblastic leukemia (ALL) with genetically modified immune cells called **chimeric antigen receptor (CAR) T cells** has researchers hopeful that this type of treatment will represent another major approach for children with cancer. One CAR T-cell therapy for childhood ALL is already pending approval by FDA, and NCI is sponsoring nearly a dozen clinical trials of CAR T-cell therapy in pediatric patients with several other types of cancer.

- In 2017, for the first time, FDA approved several **immune checkpoint inhibitors for children with cancer**. The checkpoint inhibitor pembrolizumab (Keytruda®) was approved for pediatric (and adult) patients with classical Hodgkin lymphoma that cannot be cured with existing treatments, as well as pediatric (and adult) patients with solid tumors that have specific genetic features. (See the story on page 52.) Avelumab (Bavencio®) was approved for patients age 12 or older who have metastatic Merkel cell carcinoma. FDA expanded its approval of ipilimumab (Yervoy®) to include patients age 12 or older who have advanced melanoma. NCI supported much of the preclinical and early clinical research that led to the approval of ipilimumab. The NCI Experimental Therapeutics Program (NExT) supported the early development of pembrolizumab. NCI is also sponsoring early-phase clinical trials of pembrolizumab in children with aggressive brain tumors and ipilimumab in combination with another immune checkpoint inhibitor in pediatric patients with advanced solid tumors or sarcomas.

- As part of the Cancer Moonshot, NCI is establishing a **Pediatric Immunotherapy Discovery and Development Network** to establish a collaborative research network to identify and advance research opportunities for translating immunotherapy concepts for children and adolescents with cancer toward clinical applications. As stated in the "Developing Precision Immunotherapies" section, the goals of the network are to identify new targets for immunotherapies, developing

new pediatric immunotherapy treatment approaches, and defining the biological mechanisms by which pediatric tumors evade the immune system.

Improve the Long-Term Quality of Life of Survivors of Childhood Cancer

NCI works to reduce the severity of treatment side effects for childhood cancer and to identify and address the health problems that may develop many years later, called late effects. The **Childhood Cancer Survivor Study**, funded in part by NCI, has led to a better understanding of the late effects of childhood cancer treatments and strategies to reduce these adverse effects. More than 35,000 survivors have participated in this study. Among the study's accomplishments was finding that using less cranial radiation to treat acute lymphoblastic leukemia (ALL) improves the cognitive abilities of survivors. (Read about the experience of childhood cancer survivor and pediatric oncologist Greg Aune, M.D., Ph.D., of the University of Texas Health Science Center, San Antonio, on page 61.)

KEY TAKEAWAYS

- NCI funds cutting-edge initiatives in childhood cancer research, including efforts to develop precision medicine and immunotherapy treatments, as well as efforts to improve the health and well-being of childhood cancer survivors.
- NCI advances research and facilitates collaboration against childhood cancers, filling an important gap resulting from the substantial challenges in conducting this research.
- NCI's efforts help produce more-effective, less-toxic therapies for all childhood cancers so patients not only survive, but thrive.
- NCI's longer-term goal is to use all data generated from childhood cancer research to identify children and adolescents at risk of cancer, detect cancer at the earliest stage, or prevent its development altogether.

IMPROVING OUTCOMES FOR PATIENTS WITH NF1

When 9-year-old Philip Moss ran out of treatment options for his neurofibroma tumors in April 2015, his doctors directed his family to NCI. NCI was leading the only treatment trial in the nation for children with tumors caused by neurofibromatosis type 1 (NF1), a genetic disorder in which painful and often disfiguring tumors of the nerves can grow on or under the skin. These tumors are generally benign, but about 10% of people with NF1 will develop a cancerous neurofibroma. There are currently no Food and Drug Administration-approved therapies for NF1.

Philip's experience with NF1 began when he was 6 years old, with the detection, diagnosis, and removal of a tumor on his neck. "We'd never heard of NF1 before; our world changed," said Renie Moss, Philip's mother. Unfortunately, the tumor regrew over the next few years. After additional surgery, routine imaging scans revealed that the tumor was growing again, and, over a 6-month period, it grew from the size of a ping pong ball to the size of a tennis ball. In addition, other tumors had developed. The tumor on his neck was particularly concerning because it could obstruct his airway or cause other complications. "We felt like we were one step away from disaster," recalled Renie.

Philip's doctor referred them to a phase I clinical trial at the NIH Clinical Center in Bethesda, Maryland, that was testing an experimental targeted therapy called selumetinib. The trial was led by Brigitte Widemann, M.D., chief of NCI's Pediatric Oncology Branch, and involved collaborators from Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, and the Children's National Health System.

Laboratory researchers had previously shown that mutations in the NF1 gene cause neurofibromas to grow through a chemical pathway inside cells called the RAS pathway. Selumetinib blocks a specific node in this pathway called MEK. In mouse models of NF1, MEK inhibitors reduced the growth of neurofibroma tumors. Other MEK inhibitors are safe and effective in other types of adult cancers. Based on these findings, researchers hypothesized that selumetinib might work in NF1 tumors in children.

In September 2015, Philip visited NCI for an intense medical evaluation, joined the trial, and began taking selumetinib twice a day. Because the drug is provided in pill form, Philip was able to return home for ongoing treatment and was monitored by his local pediatrician. He and his family learned to cope with the initial side effects of treatment, which included fatigue, headaches, and nausea. One year after joining the trial, Philip's tumors were 36% smaller.

Although this trial was a small early-phase study, Philip was among the 71% of children whose tumor volumes decreased by more than 20%. "We saw tumor shrinkage in nearly every patient," Brigitte remarked. "The shrinkage was measurable…something we had never seen before" among NF1 patients. These promising results are now being pursued in a phase II study.

Philip remains in the trial, and the tumor on his neck has shrunk by half. "Kids don't ask what's wrong with him anymore," said Renie. "It's meant the world to him and to our family." Renie acknowledged the years of research that led to this trial. "Someone was planting the seeds in NF1 research so we would benefit from that work now."

PHILIP MOSS

Neurofibroma Survivor
Alabama

USING TANDEM TRANSPLANTS TO TREAT NEUROBLASTOMA

JULIE PARK, M.D.

Bushnell, Towne, and Wilkerson Endowed Chair in Pediatric Neuroblastoma, Seattle Children's Hospital

Professor of Pediatrics, University of Washington School of Medicine

Associate, Clinical Research Division, Fred Hutchinson Cancer Research Center

For many years, less than half of children diagnosed with high-risk neuroblastoma, a cancer that starts in immature nerve cells, would be expected to live 5 or more years after diagnosis. Pediatric oncologist and researcher Julie Park has devoted her career to try to change that. In 2016, Julie and her colleagues demonstrated encouraging improvements using a new approach to treat high-risk neuroblastoma in an NCI-sponsored clinical trial that changed the way the disease is treated in the United States. The trial was conducted by the Children's Oncology Group (COG), part of NCI's National Clinical Trials Network.

One of the 652 children who participated in the trial was Katie Belle of Seattle, who was 3½ years old in 2009, when doctors found a baseball-sized tumor in her abdomen that turned out to be high-risk neuroblastoma. Katie was given a 35% chance of survival, and, on the advice of doctors, her parents immediately enrolled her in the COG trial. "When we signed Katie up, there didn't seem to be a lot of novel, promising ideas to pursue," said her mother Jennifer Belle, who now serves as a patient advocate on COG's Neuroblastoma Committee.

Before the COG trial, the standard treatment for high-risk neuroblastoma was a single-transplant approach that involved high-dose chemotherapy to destroy as many cancer cells as possible, followed by an autologous (self-donating) blood stem cell transplant. The stem cell transplant is needed because the intense chemotherapy also destroys blood-forming stem cells in the patient's bone marrow. The stem cells used for the transplant are collected from the patient's blood and then given back to the patient once the chemotherapy is completed. The transplanted cells then repopulate the patient's bone marrow and restore its ability to produce red and white blood cells and platelets. Prior clinical trials conducted by COG demonstrated that this treatment approach improved the 5-year survival rate for children with high-risk neuroblastoma from 25% in the 1990s to just less than 50% by the early 2000's.

The new approach in the recent COG trial was to double-up that treatment, with the hopes of increasing the percentage of patients who would benefit from this intense therapy. In the trial, one group of patients received the standard treatment (chemotherapy and a stem cell transplant) and another group received the experimental treatment (chemotherapy and a stem cell transplant followed by another round of chemotherapy and a second, or tandem, stem cell transplant). After 3 years of follow-up, 61% of the patients who received a tandem transplant were alive and cancer-free, compared with 48% of those who received only a single transplant.

Katie was among the patients who received a tandem transplant. More than 5 years later, she remains cancer free. Although she is generally in good health now, Katie did experience side effects from the treatment, including sterility and thyroid dysfunction. Jennifer worries about her future. "We don't know what the other long-term complications will be," she said. Julie added, "The therapies for high-risk neuroblastoma are among the most toxic therapies given to kids."

Tandem transplants have now become the standard of care for high-risk neuroblastoma. "Through continued research, we keep moving the needle and improving survival," Julie reflected. "The next step is to find treatments that will be less toxic and more effective." To this end, COG researchers hope to capitalize on advances in molecular biology and immunology research to find additional targets and improve the quality of life for children like Katie.

SEARCHING FOR LESS TOXIC TREATMENTS

Advances in cancer treatment mean that, today, more than 4 out of 5 children diagnosed with cancer will survive and remain cancer free for at least 5 years after diagnosis. Many of these children will ultimately be considered cured of their cancer. However, the chances of either developing a life-threatening health problem or dying early as a result of their treatment approaches 60% by age 50. Potential late effects include cardiovascular disease, second cancers, and premature menopause.

As a childhood cancer survivor, pediatric oncologist, and cancer research advocate, Greg Aune knows firsthand that cancer is not an acute disease but a lifelong problem. At age 16, he was diagnosed with Hodgkin lymphoma and was successfully treated after undergoing a year of chemotherapy and radiation treatments. However, he has experienced many late effects from his treatment, including infertility, stroke, and life-threatening heart disease. "My story is one of persistent personal frustration with the toxicities of chemotherapy and radiation," said Greg. In fact, his cancer experience is what motivated him to become a pediatric oncologist and physician–scientist.

Anthracyclines, some of the most commonly used chemotherapy drugs in pediatric oncology, can severally damage the heart. Greg's research focuses on identifying biomarkers of toxicity in the heart caused by these powerful drugs. Understanding this relationship will help researchers develop new strategies for detecting, preventing, treating, and managing cardiac disease in the large number of pediatric cancer survivors treated with anthracyclines.

The goal of current pediatric oncology research is to identify better targeted therapies that are less toxic. "My hope is that we're at a point where we can not only offer children with cancer an opportunity for a cure, but a long life free of debilitating health conditions," said Greg. "In no other field of medicine would the late effects we see in pediatric cancer be considered an unqualified success," he added.

Until less-toxic therapies are developed, it is imperative for health care teams to educate the 420,000 U.S. survivors of childhood cancer about the possible late effects of their treatment and empower them to be active participants in their lifelong post-cancer health care.

GREGORY AUNE, M.D., PH.D.

Stephanie Edlund Distinguished Professor in Pediatric Cancer Research and St. Baldrick's Scholar, Greehey Children's Cancer Research Institute, University of Texas Health Science Center, San Antonio

ADVANCING PUBLIC HEALTH IN CANCER

Cancer has been recognized as a major public health problem in the United States for nearly a century. Today, despite the steady decline in cancer mortality observed over the past two decades, it is the leading cause of death from disease among Americans under the age of 85. By 2020, it is projected to be the number one cause of death from disease among all age groups. However, many cancers and cancer deaths can be avoided by maintaining a healthy lifestyle and receiving recommended cancer screenings and preventive vaccinations.

NCI supports research focused on improving the delivery of cancer care and designing interventions at the individual and population levels to improve cancer prevention, screening, treatment, and survivorship. Some areas of opportunity include improving the quality of life of cancer survivors; understanding how body weight and physical activity influence cancer risk and outcomes; further reducing tobacco use; and delivering high-quality cancer prevention, screening, and treatment to all regions of the country.

Improving the Quality of Life of Cancer Survivors

The number of long-term cancer survivors has grown dramatically over the past several decades, a trend that is expected to continue as diagnosis and treatments improve. Today, approximately 70% of people live 5 years or more following a cancer diagnosis, compared with about 50% in the 1970s. In 2016, the estimated number of cancer survivors in the United States exceeded 15 million, more than twice the estimated 7 million in 1992.

In addition to the growing number of survivors, the proportion who are age 65 years or older will expand rapidly as the U.S. population continues to age. By 2040, it is estimated that nearly half of cancer survivors will be age 75 or older.

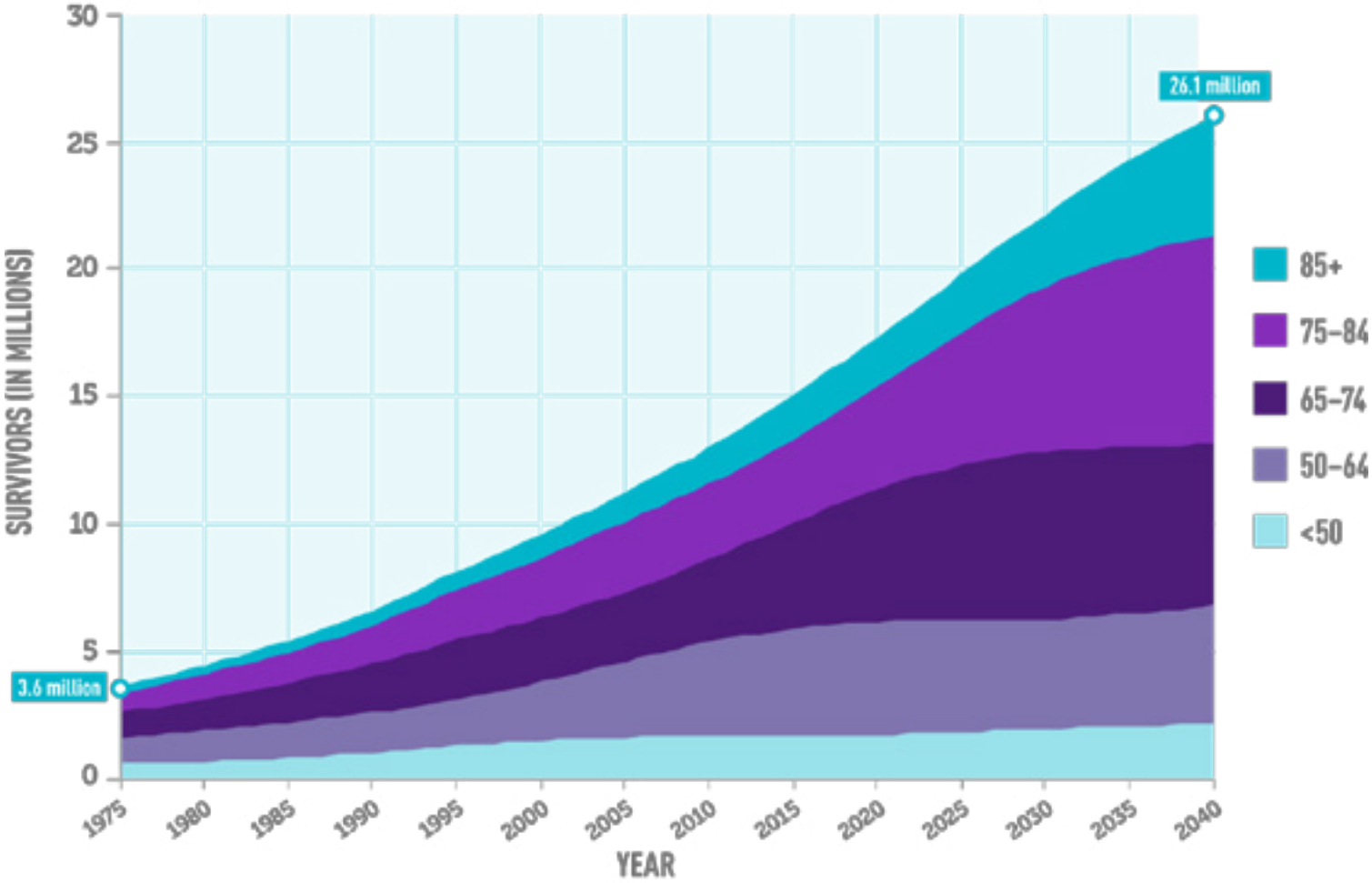
With this increase in survivorship has come an awareness that many cancer survivors have health problems, caused by their cancer or its treatment, that may require additional and, perhaps, ongoing care. Satisfactorily addressing these health problems in older survivors may be complicated by the development of other conditions associated with aging. Meanwhile, all of this is occurring against a backdrop of projected shortages of oncologists and primary care physicians, who are the main providers of medical care for cancer survivors.

Consequently, research to understand and find ways to address the unique needs of cancer survivors, especially older survivors, is critical and a high priority for NCI.

CHALLENGES THAT CANCER SURVIVORS FACE

- Risk of recurrence
- Increased risk of second primary cancer
- Reduced quality of life
- Economic burden (financial toxicity)
- Treatment side effects (cardiotoxicity, cognitive challenges)
- Emotional distress (depression, anxiety/uncertainty, altered body image, survivor's guilt)
- Denial of health and/or life insurance
- Physical problems
- Loss of fertility and/or diminished reproductive health
- Difficulty maintaining or finding employment
- Barriers to health care (high insurance and out-of-pocket costs for health care, lack of coordination of health care, and limited access to specialty care)

A Surge in Older Survivors: Estimated Number of U.S. Cancer Survivors by Age Group



Source: Bluethmann SM et al. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.

THE VISION

To make available effective interventions that mitigate the short-term and long-term adverse effects of cancer and its treatment and greatly improve the well-being and quality of life of cancer survivors

THE APPROACH

- Support research to identify and understand the factors that cause—or increase susceptibility to—the short-term and long-term adverse effects of cancer and its treatment
- Support research to develop effective interventions to reduce or prevent these adverse effects and improve the well-being and quality of life of cancer survivors

Research Priority

Identify and Alleviate the Adverse Effects of Cancer and Its Treatment

Cancer and its treatment are associated with substantial short-term and long-term adverse side effects that can diminish the well-being of survivors. NCI funds research to develop new treatments that cause fewer adverse effects. In addition, NCI supports research to identify factors that cause or increase susceptibility to the harmful effects of cancer and its treatment and to develop interventions to reduce or prevent their occurrence.

Several examples of NCI's accomplishments and efforts include:

- NCI's portfolio of symptom management clinical trials is coordinated through the **NCI Community Oncology Program (NCORP)**. NCORP sponsored a clinical trial testing duloxetine (Cymbalta®) in breast cancer survivors who were taking **aromatase inhibitors**. Findings from the trial, reported in 2017, showed that duloxetine, which is approved to treat depression and anxiety, fibromyalgia, and nerve pain caused by diabetes, reduced musculoskeletal pain by an average of 46%. These findings are important because musculoskeletal symptoms lead some patients to discontinue these life-saving aromatase inhibitors.

- The **Detroit Research on Cancer Survivors** study, launched in 2017, is the largest study to date of African-American cancer survivors in the United States. It will include 5,560 participants and investigate major factors that affect cancer recurrence, mortality, and quality of life among these cancer survivors.

- NCI's **National Clinical Trials Network (NCTN)** is developing more trials targeted at older patients, particularly those with other health conditions, such as heart disease or diabetes. The results of these trials should help doctors **develop age-appropriate treatment plans** and potentially reduce long-term treatment-related side effects. They may also provide much-needed information about resources and programs necessary for cancer survivors in long-term recovery.

NCI also supports survivorship research conferences and the development of online tools for survivors, including the **Springboard Beyond Cancer** website. The website is a joint venture of NCI and the American Cancer Society, designed to improve survivors' self-management of cancer-related symptoms and treatment side effects, with a focus on identifying strategies and skills training. The development of this website was informed by cancer survivorship research and health behavior interventions.

KEY TAKEAWAYS

- NCI sponsors research to identify and understand factors that cause or increase susceptibility to the adverse effects of cancer and its treatment.
- NCI-funded researchers are striving to develop effective interventions to reduce or prevent these harmful effects and improve the well-being and quality of life of cancer survivors.

Understanding the Influence of Body Weight and Physical Activity on Cancer Risk and Outcomes

Numerous epidemiologic studies have linked obesity and physical inactivity with increased risks of more than a dozen types of cancer. Research also suggests that physically active cancer survivors have fewer or less-severe side effects from treatment and an improved quality of life compared with those who are inactive. Associations between exercise and reduced rates of cancer recurrence and mortality have also been reported. However, more research is needed to understand the biological mechanisms by which body weight and physical activity influence cancer risk and patient outcomes. This knowledge can then be translated into effective interventions.

THE VISION

To prevent more cancers and improve the quality of life of survivors by reducing obesity and physical inactivity

THE APPROACH

- Support research to better understand how body weight and physical activity influence cancer risk and outcomes for cancer patients and survivors

Research Priority

NCI funds a wide range of research to learn how body weight and physical activity modify cancer risk and outcomes, and NCI-funded researchers use the acquired knowledge to design and test new interventions.

Understand the Effects of Weight and Physical Activity on Cancer Risk and Patient Outcomes

The biological mechanisms by which body weight and physical activity influence cancer risk and patient outcomes are not well understood. Moreover, traditional epidemiologic studies are limited in their ability to determine how strongly these factors influence cancer-related outcomes because they rely on people's ability to accurately recall or record their weight at specific ages as well as their dietary intakes and amounts of physical activity over time. Consequently, stronger study designs, such as randomized controlled trials when feasible, and more accurate survey instruments are needed. Therefore, NCI supports research in the laboratory and the clinic to address these issues, with the goal of ultimately translating the knowledge gained into effective interventions for those at risk of cancer and for cancer survivors.

Examples of NCI-funded research in this area include:

- The **Transdisciplinary Research on Energetics and Cancer (TREC)** initiative, which catalyzed research on the biological, behavioral, sociocultural, and environmental influences that affect nutrition, energy balance (the ratio of calories consumed

to calories burned), body weight, physical activity, and cancer risk. TREC, which was funded in 2005 and 2010, enabled the creation of research partnerships that otherwise would not have been possible. Some TREC studies incorporated animal and human models to identify and understand the relevant biomarkers and physiological effects of exercise, sedentary behavior, diet, and, cancer. The role of sleep in obesity and energy balance was also explored.

Two of the many research advances that have emerged from TREC are:

- **An increased understanding of how obesity influences chemotherapy effectiveness**: TREC researchers at the Children's Hospital Los Angeles and the University of Southern California developed novel preclinical models to understand the mechanisms underlying the increased risk of relapse observed among obese children with acute lymphoblastic leukemia (ALL). They determined that adipocytes (fat cells) impair the response of leukemia cells to chemotherapy in a manner that is independent of cell–cell contact. These findings have led to a clinical trial of personalized dietary and exercise interventions in children and adolescents with newly diagnosed ALL to reduce body fat and improve treatment responses.

- **A greater understanding of the potential for exercise to reduce the increased risk of breast cancer associated with delayed childbearing**: Research support from TREC enabled a team of researchers from the University of Pennsylvania, Harvard University, Washington University in St. Louis, and Kaiser Permanente Northern California to develop an animal model to study the protective effects of exercise on the breast cancer risk associated with delayed childbearing. The researchers found that exercised rats had a longer time to tumor development, a smaller tumor burden, and less abnormal proliferation of breast tissue (ductal hyperplasia) than rats that had not been exercised.

Other TREC accomplishments include new statistical modeling methods, a system for coding health messages in the media, new dietary measurement tools, and databases for physical activity and sleep measures. Ongoing research is exploring whether obesity, which is a risk factor for postmenopausal breast cancer, influences immune cell populations in the breast tumor microenvironment. Ideas for another TREC renewal (i.e., TREC 3) are currently in development.

- **Weight loss, diet, and exercise interventions for cancer survivors** to identify those interventions that are most effective and understand how they influence outcomes for survivors. The randomized Lifestyle, Exercise, and Nutrition (LEAN) Study, described on page 69, highlights this type of research.

KEY TAKEAWAY

- NCI sponsors research that will increase the understanding of how diet, body weight, and physical activity influence cancer incidence and outcomes and translate the knowledge gained into effective interventions for cancer patients, survivors, and those at risk.

RUNNING (AND EATING) AWAY FROM CANCER

Sue Wharfe was diagnosed in 2011 with stage II breast cancer. Her doctors at Yale Cancer Center, where she received treatment, referred her to a research study on nutrition and exercise for breast cancer survivors. Sue jumped at the chance to participate. She hoped it would help her to lose weight and improve her diet. "I was the type of person who would join a gym, feel good about joining, but then never go. I had good intentions but following through with them was a challenge," she explained.

Research shows that obesity is associated with worse survival from breast cancer, but more research is needed to develop and implement methods to help cancer survivors make positive lifestyle changes. Sue was one of 100 women who participated in a study led by Melinda Irwin, Ph.D., M.P.H., professor of epidemiology at Yale University, aiming to address this question. The study—called the Lifestyle, Exercise, and Nutrition Study, or LEAN—showed that in-person and telephone counseling led to clinically significant weight loss among participants. The researchers also gained clues about the biological effects of weight on breast cancer. Participants who received counseling experienced a 30% decrease in C-reactive protein, a marker of systemic inflammation that is associated with poorer outcomes in women with breast cancer.

Sue was randomly assigned to the in-person intervention. With encouragement from the registered dietician and oncology nutrition specialist assigned to her in the study, Sue took up running with a friend, starting with 20 minutes a day, and began to feel the benefits of the activity in about 3 weeks. From a diet that contained too much fat, she switched to a "rainbow plate" with more fruits and vegetables. She benefited from the intervention, which supported her as she was trying to lose weight, a change she appreciates to this day.

The changes also helped with the stiffness and achiness in her joints that accompanied her aromatase inhibitor therapy, which she recently learned she needs to continue taking for another 5 years. In fact, additional NCI-funded research by Melinda's team found that exercise reduces joint pain associated with aromatase inhibitors.

LEAN was enabled by NCI's Cancer Center Support Grant to Yale, which provides resources to support exceptional clinical care and conduct transdisciplinary research. Melinda is appreciative of NCI, which has enabled her to conduct some of the largest trials investigating the interactions between weight, diet, and physical activity in relation to cancer. She is also part of NCI's Transdisciplinary Research on Energetics and Cancer (TREC) initiative. "NCI is the only organization that provides longer-term funding to support this type of research, which aims to change paradigms with the goal of lowering people's risk of developing or dying from cancer," said Melinda.

Sue can attest to the efficacy of this intervention. Years later, she continues to jog and eat healthfully, still mindful of the better behaviors she learned from Melinda's study. Her good habits have rubbed off on her husband and kids, too. She doubts she would have made these lifestyle improvements without LEAN. "It has led to a better, healthier life," she added.

SUE WHARFE

Breast Cancer Survivor
Connecticut

Reducing Tobacco Use Before and After a Cancer Diagnosis

At least 20 different types of cancer have been linked to tobacco use, and more than 160,000 cancer deaths each year in the United States are attributable to smoking. Major reductions in tobacco use among American adults—from a high of 42% of the adult population in 1965 to about 15% today—have lowered the number of deaths from lung cancer and other tobacco-related diseases; however, lung cancer still claims more lives among U.S. men and women than any other cancer type.

Cancer patients who continue to smoke after diagnosis may face additional tobacco-related harms. For example, NCI-funded research has shown that continued smoking increases the risk of second cancers in patients with head and neck cancer, increases risks of recurrence and reduced survival in patients with prostate cancer, and increases risks of death from breast and respiratory tract cancers in women diagnosed with breast cancer. Other NCI-funded research has shown that cancer patients who continue to smoke experience a greater burden of treatment-related side effects than nonsmokers, which may lead to treatment interruptions, reductions in treatment doses, and delays in treatment that can, in turn, compromise treatment effectiveness and reduce survival. However, more research is needed to fully understand the impact of continued smoking on cancer patients, particularly on the effectiveness of cancer therapy.

Additional research and resources are also needed to further reduce the harms of tobacco use among individuals who have not been diagnosed with cancer, especially those in at-risk populations for tobacco uptake, including the young and the socioeconomically disadvantaged.

THE VISION

To eliminate smoking, and the cancers and other harms it causes, to improve public health

THE APPROACH

- Support research on tobacco prevention and cessation interventions—especially those aimed at vulnerable populations, including the young and the socioeconomically disadvantaged, who are at increased risk of tobacco use
- Support research to implement and sustain evidence-based tobacco cessation programs, in cancer centers and other medical settings, to reduce tobacco use by cancer patients

Research Priorities

Support Research on Tobacco Prevention and Cessation

To help guide NCI's tobacco control research agenda through the year 2025, the institute established the **Tobacco Control Research Priorities Working Group** in 2015. This group, led by Michael Fiore, M.D., M.P.H., M.B.A., of the University of Wisconsin

School of Medicine and Public Health, presented its report to NCI's Board of Scientific Advisors in 2016. (Read about Michael's perspective on page 72.) The working group's recommendations included a call for focused efforts to improve the effectiveness and accessibility of tobacco prevention and cessation interventions and to discourage tobacco use by vulnerable populations. NCI is well positioned to support the working group's recommendations.

Implement Effective Tobacco Prevention and Cessation Interventions

The development and implementation of effective tobacco cessation interventions for cancer patients and those at increased risk of cancer is a high priority for NCI. For example, the institute:

- **Supports tobacco cessation at NCI-Designated Cancer Centers**: Evidence-based tobacco cessation interventions designed for individuals without cancer should be offered as part of the coordinated care of all cancer patients. However, comprehensive tobacco cessation programs are not currently available at all NCI-Designated Cancer Centers that provide patient care services. Therefore, NCI is making supplemental funding available to help cancer centers plan, implement, evaluate, and sustain tobacco cessation programs for cancer patients who smoke. In addition, NCI has awarded grants to six cancer centers to conduct research on the design and implementation of tobacco cessation interventions for patients undergoing lung cancer screening with low-dose CT scans.
- Hosts the **Smokefree.gov** website to make information and resources about smoking cessation available to the public, health professionals, and researchers. In 2016, 4.5 million smokers interacted with Smokefree.gov.

KEY TAKEAWAY

- NCI supports research to develop and implement evidence-based measures to reduce the use of tobacco products among all individuals, including populations that are vulnerable to the initiation of tobacco use and patients who are undergoing or have completed active cancer treatment.

MICHAEL FIORE, M.D., M.P.H., M.B.A.

Hilldale Professor of Medicine, University of Wisconsin School of Medicine and Public Health

Founder and Director, University of Wisconsin Center for Tobacco Research and Intervention

WORKING TO REDUCE THE CANCER BURDEN CAUSED BY TOBACCO

Every year, 70% of smokers in the United States visit a health care professional. Many, however, leave without receiving any smoking cessation assistance. Approximately half of smokers diagnosed with cancer continue to smoke, and only some health care centers provide these patients with services to quit. "This is a missed opportunity to help people become healthier and live longer," said physician and researcher Michael Fiore.

Tobacco use in the United States continues to cause unparalleled harm to the nation's health, directly causing one out of every five deaths. Moreover, tobacco causes at least 20 different types of cancer, including up to 90% of all lung cancers. Cigarette smoking is the main culprit, being responsible for more than 480,000 deaths per year in this country, including nearly 42,000 deaths from exposure to secondhand smoke. Michael predicts that "eliminating smoking in America would, over time, reduce all cancer deaths by almost one-third."

As a leader in tobacco control, Michael helped to spearhead a working group of the NCI Board of Scientific Advisors that recommended research priorities for this field. The group's 2016 report discussed a wide range of research gaps. One of these was optimizing the effectiveness of the evidence-based tobacco cessation interventions that already exist. The report also highlighted groups that disproportionately bear the burden of cancer and other health consequences of continued tobacco use.

NCI has a long history of supporting tobacco control research and launched several new activities in 2017 relevant to the priorities the working group identified. These include additional funding to NCI-Designated Cancer Centers to bolster smoking cessation activities and focused efforts to reduce tobacco use by vulnerable groups, including the young, the socioeconomically disadvantaged, and individuals with mental health issues or HIV.

Michael is hopeful about NCI's response to the working group's recommendations and commitment to reducing the cancer burden in the United States. "Recognizing that tobacco use is a chronic disease—and not just a bad habit—informs our ongoing research to identify and implement the best prevention and cessation strategies," he said.

Delivering High-Quality Cancer Care to All Americans

NCI supports research to understand and improve how cancer care is delivered in the United States. The ultimate goal of this research is to ensure that high-quality cancer care is available and accessible to all Americans wherever they live.

Developing, implementing, and sustaining state-of-the-art cancer prevention, screening, and treatment programs for rural populations, will be particularly challenging. Rural populations often face substantial barriers in accessing quality health care due to a shortage of doctors, lengthy distances to medical facilities, limited transportation options, and other factors. In addition, rural populations frequently have high rates of tobacco use, poverty, poor health literacy, and drug and alcohol abuse, which contribute to higher cancer risks and poorer health outcomes.

THE VISION

To make state-of-the-art cancer care available and accessible to all Americans

THE APPROACH

- Support research to identify factors that influence cancer care delivery in all regions of the United States and its territories
- Support research to improve the delivery of high-quality cancer care to the American public

Research Priority

Identify and Address Factors that Influence the Delivery of Quality Cancer Care

NCI supports research on the delivery of cancer care through its **Healthcare Delivery Research Program** and the **NCI Community Oncology Research Program**. This research includes studying barriers to the implementation of evidence-based cancer prevention, screening, and treatment methods; recommended follow-up care for cancer survivors; and psychosocial support programs for patients and their caregivers. The ultimate goal of this research is to optimize the delivery of high-quality cancer care to all Americans, thereby helping to reduce the burden of cancer in the United States. Some of NCI's activities in this area include:

- Supporting telecommunications research on the use of broadband technologies to promote improved cancer prevention and care in both rural and urban areas. This research, for example, led to the online program **A Smoking Prevention Interactive Experience (ASPIRE)**, which is aimed at middle and high school students.

- Working with other organizations through the Centers for Disease Control and Prevention's **National Comprehensive Cancer Control Program (NCCCP)**. NCI and the other NCCCP members support comprehensive cancer control activities in U.S. states, territories, Pacific Island jurisdictions, and tribes and tribal organizations.

Activities include efforts to increase HPV vaccination uptake, increase colorectal cancer screening, and increase availability of tobacco cessation services for cancer survivors—areas that are described in previous sections of this *Annual Plan and Budget Proposal*.

- As NCI strengthens its efforts in cancer control and prevention, the needs of **Native American and Alaska Native** populations are particularly important. These populations have unique needs and concerns that can be challenging to address. For example, Native Americans and Alaska Natives have higher incidence and death rates from certain cancers than other populations groups. This population is diverse, and culturally relevant prevention and early detection efforts are needed. NCI is working to address these needs.

KEY TAKEAWAY

- NCI supports health care delivery research, infrastructure, and partnerships that will increase accessibility to high-quality cancer care to all individuals in the United States, including those in minority and underserved rural populations.

ADDRESSING CANCER DISPARITIES IN APPALACHIA

"For people struggling to make ends meet, the last thing on their minds is health care," said Electra Paskett, who has devoted her 30-year career to addressing cancer disparities experienced by underserved groups in the United States. "The question we want to answer is how to reach them," she said.

Electra's efforts to address cancer disparities through science and community partnerships, which NCI has supported over the last two decades, have led to important improvements in cancer screening and care in rural and low-income populations where cancer rates have remained stubbornly high. Populations in the Ohio Appalachian region and inner-city African Americans, in particular, have benefited from her studies.

In the Appalachian areas of Ohio, Kentucky, Pennsylvania, Virginia, and West Virginia, the rates of lung, cervical, and colorectal cancer incidence and mortality are higher than anywhere else in the United States. "It's all about figuring out why," said Electra. To identify the causes of these disparities and develop ways to reduce them, she conducts research to develop and test interventions.

Her approach includes partnership building with local clinicians and public health officials and, most importantly, with members of the community. "The people who live there in those communities know what strategies work best for them," explained Electra. This community-based participatory research approach means she often takes road trips into the heart of Appalachian country.

In these less-populous areas, she meets with locals, listens to their stories, and asks for their perspectives on how to address their higher-than-average cancer incidence and mortality rates. With their assistance, Electra has successfully pinpointed public health flaws and gaps.

Her research has tested such initiatives as working with local churches to promote healthy eating and exercise, conducting outreach to parents and clinicians to improve rates of HPV vaccinations among adolescent girls, and implementing mammogram vans to make breast cancer screening more accessible. By working with communities and implementing culturally sensitive strategies, Electra has found that people will be more proactive about their health needs and even adopt healthier behaviors, such as regular cancer screenings, when appropriate programs and incentives are put into place.

ELECTRA PASKETT, PH.D.

Director and Marion N. Rowley Professor of Cancer Research, Division of Cancer Prevention and Control, The Ohio State University College of Medicine

STRENGTHENING THE CANCER RESEARCH ENTERPRISE

NCI leads the national effort against cancer in many ways. NCI sustains the cancer research workforce through training and research grant support. The institute also supports infrastructure to care for patients and conduct clinical trials, prevent cancer and develop better treatments by understanding the biological and molecular mechanisms that promote cancer growth, and promote data sharing to hasten progress in cancer research for all Americans and the rest of the world. Resources developed by NCI help investigators maximize their research efforts. Research at NCI focuses on high-risk studies and areas of unmet need. Together, these efforts are aimed at improving cancer prevention, detection, and treatment, with the goal of producing better outcomes for patients and those at risk for cancer.

Supporting Scientists at Every Career Stage

A strong workforce of researchers who are passionate about cancer research and are well-supported can make discoveries faster and translate them more efficiently into new ways to prevent, detect, and treat cancer. To address this need, NCI supports a diverse scientific workforce over the course of their careers—as high school, college, and graduate students; research and clinical fellows; early career researchers; and established investigators. NCI supports individual investigators as well as collaborative research teams.

Training the Next Generation of Cancer Researchers

NCI supports the next generation of cancer scientists, who will make the paradigm-shifting discoveries of the future.

- The middle and high school years are important in shaping students' perceptions about possible future careers, and two programs showcase how NCI is providing training opportunities to students at this impressionable stage.
    - The **Continuing Umbrella of Research Experiences (CURE)** program promotes diversity in the cancer and cancer health disparities research workforce by providing training and career development support for underrepresented minorities. CURE emphasizes mentorship, provides protected time to gain research experience, and creates training opportunities to develop career skills. CURE provides support to high school students and to undergraduate and graduate students, and in 2014, the program began engaging students at the middle school level. Over the past two decades, the program has supported more than 3,000 scholars from almost every state across the country. (Read about former CURE trainee Chanita Hughes-Halbert, Ph.D., of the Medical University of South Carolina, on page 86.)
    - The **Werner H. Kirsten Student Intern Program** has brought more than 1,000 high school students to NCI's campus in Frederick, Maryland, for a summer internship that continues part-time throughout their senior year. The interns gain hands-on laboratory research training or experience in scientific support areas, including communications and information technology. More than half of the students in the program have gone on to careers in health, medicine, science, or education. The program recently celebrated its 25th anniversary

and received an Award of Excellence from the Maryland State Department of Education in 2017.

- The **NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00)** helps graduate students who are near the end of their graduate education and wish to pursue a research career move into postdoctoral studies. The program helps students to develop a well-defined career path more quickly by preparing them for other awards that will lead to independent, tenure-track, or equivalent faculty positions.

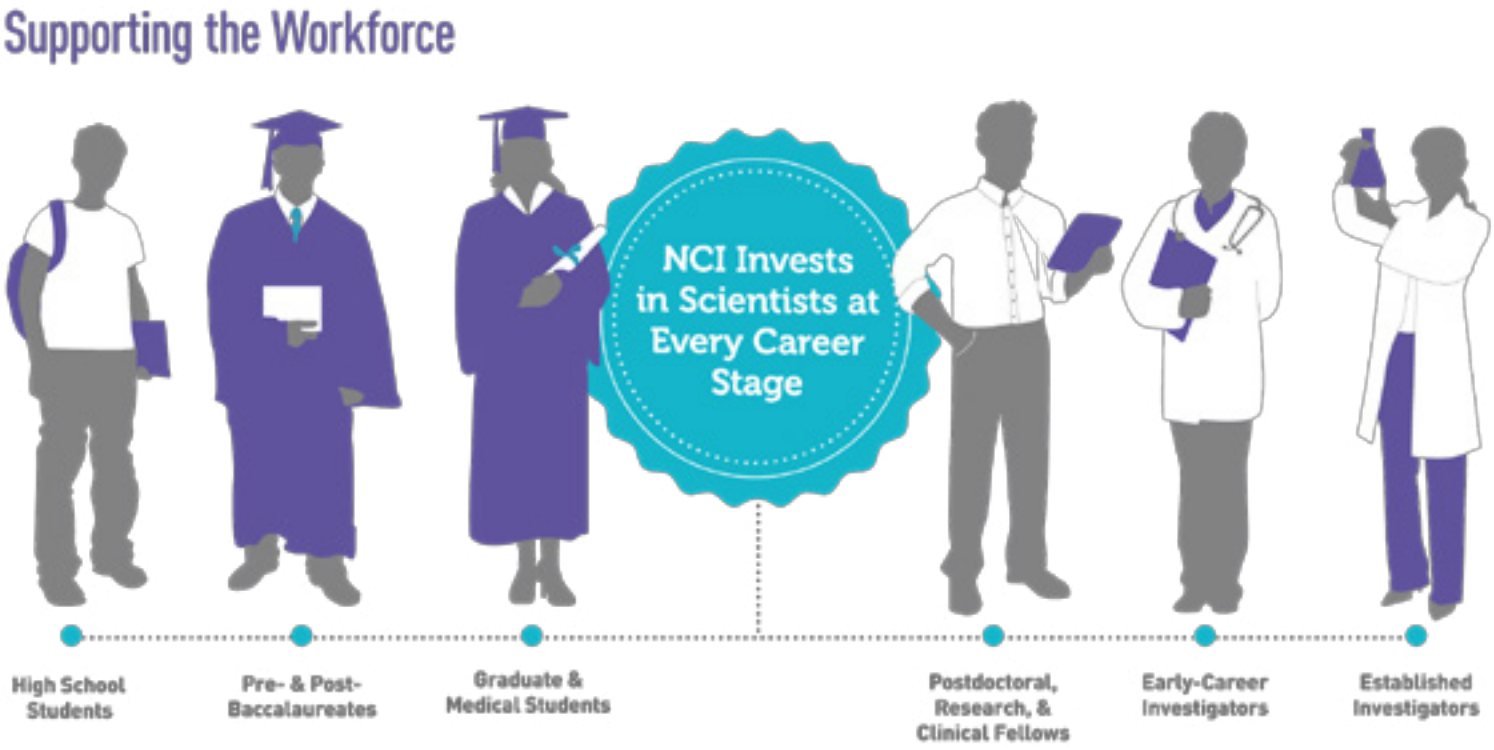
Investing in Early-Career and Established Investigators

Everything NCI does focuses on supporting the best science to improve the outlook for patients and their families. To do this, NCI seeks to recruit outstanding investigators and provide them with support throughout their careers in cancer research. A few ways in which NCI does this include:

- **Focusing on investigator-initiated research**: More than 40% of the total NCI budget supports research project grants, an important mechanism for advancing the ideas of an individual or small group of investigators at all stages of their career. Supporting investigator-initiated research is a high priority for NCI because the unique insights and expertise of investigators allow research to expand into previously unforeseen but potentially productive areas. Between 2013 and 2015, NCI increased support for new awards from $400 million to $500 million per year and continues to sustain the increase. In addition, 2015 and 2016 were the first years since 2004 and 2005 that NCI provided full support for noncompeting grants (funding for the next budget period within an approved project period) for 2 years in a row. This support is greatly valued for assuring continued advancement in all areas of cancer research.

- **Supporting new and early-stage investigators**: Scientists starting independent research positions are at a critical stage in their careers. NCI supports these innovators of the future through grants, such as mentored career development awards, and other activities designed to enhance their ability to succeed in cancer research. One new activity, the principal investigator workshops conducted by NCI's division leadership and program staff, connects new R01 grant recipients with NCI staff responsible for administering their grant. Approximately 20%–24% of all R01 awards are provided to new and early-stage investigators, and 40% of R21 grant awards are made to new investigators.

- **Finding new approaches to fund researchers**: The NCI Outstanding Investigator Award (R35), which is given to principal investigators who have a history of significant research accomplishments and outstanding productivity, is an example of a new approach to fund researchers. The R35 award provides stable funding for a longer period than that afforded by a traditional R01 award. The funding stability provided by this award encourages accomplished investigators to take on higher-risk and potentially higher-reward research projects. The R35 program began in fiscal year (FY) 2015 with awards made to 43 prominent investigators, followed by 35 new awards in FY 2016 and 43 in FY 2017.



Providing Infrastructure and Resources for Cancer Research and Patient Care

NCI supports the cancer research community through an infrastructure that connects investigators working at major academic research centers, in community settings, within NCI and other federal agencies, and at private-sector companies. NCI's collaborative efforts with partners across the community put patients at the forefront by ensuring that scientists and clinical researchers are equipped to make discoveries and test ideas that advance cancer research and clinical care across the United States.

Sustaining NCI-Designated Cancer Centers

The **NCI-Designated Cancer Centers Program** constitutes a major component of the national cancer research enterprise. NCI-Designated Cancer Centers meet rigorous standards for research focused on developing new and better approaches to cancer prevention, diagnosis, and treatment. Acquiring the "NCI-designated" status is a major achievement, and cancer centers that receive it are highly valued by their communities because they are recognized as providing state-of-the-art, evidenced-based cancer care. There are currently 69 of these cancer centers in the United States. In recent years, NCI has increased the size of the Cancer Center Support Grants that support the infrastructure needed by researchers at a cancer center—such as centralized shared resources—and that create a focused transdisciplinary research environment. The

program was established with a vision of having an NCI-Designated Cancer Center within 200 miles of every person residing in the United States.

Facilitating Cancer Clinical Trials

NCI has a long history of supporting all phases of clinical trials, from small early-phase trials that seek to determine the safety of new interventions to large trials that compare new interventions with the current standard approach.

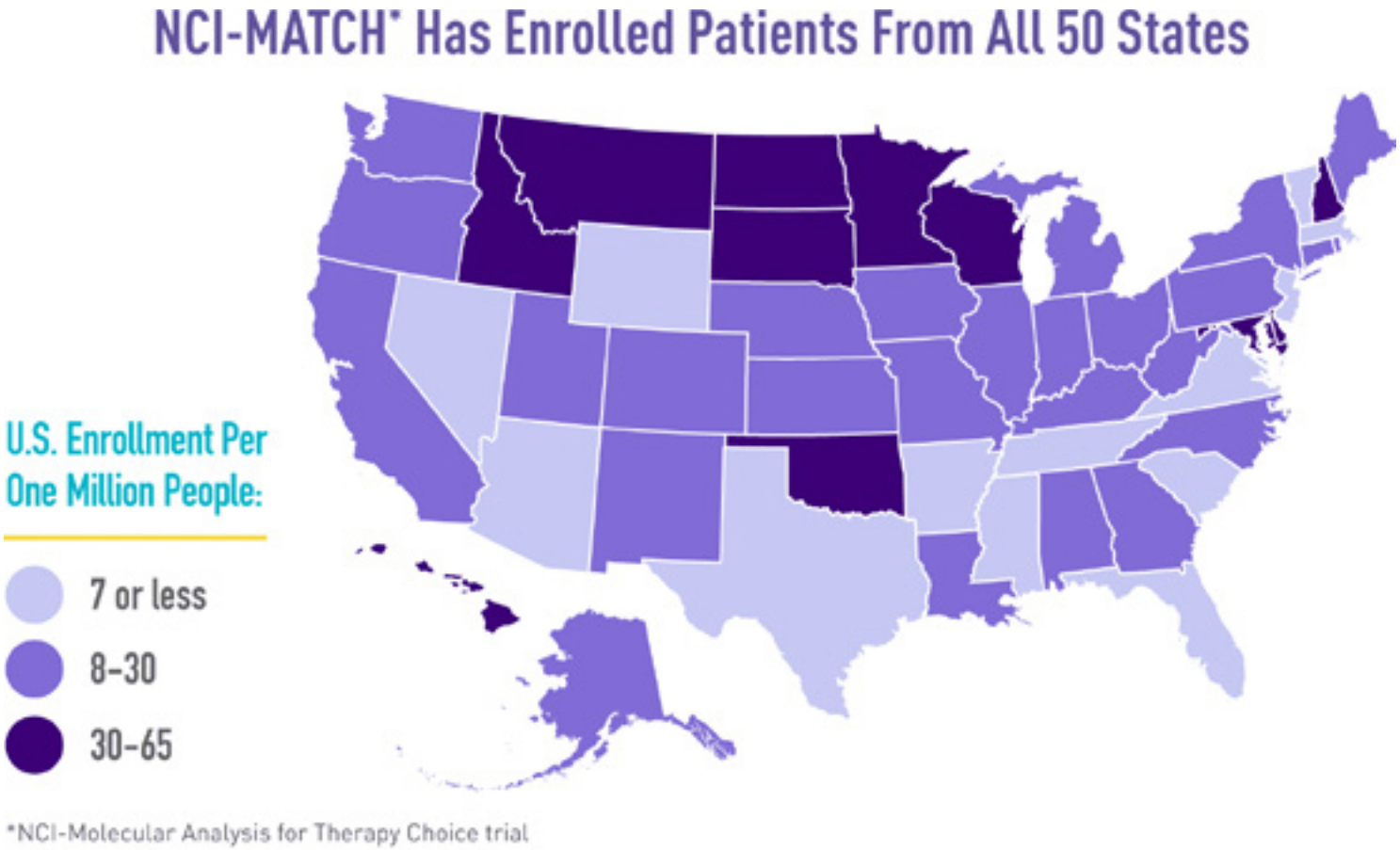
- NCI's **National Clinical Trials Network (NCTN)** serves as the cornerstone of the institute's clinical trial enterprise. NCTN provides streamlined mechanisms for conducting cancer clinical trials throughout the United States. The network includes five U.S. clinical trial research groups and several international member sites that contribute to the approximately 2,400 NCTN sites enrolling patients in clinical treatment trials, including precision medicine clinical trials such as the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) and NCI-COG Pediatric MATCH trials.

  Examples of NCTN trials with recently reported results include:

  - A trial demonstrating that, after 10 years of follow-up, progression-free and overall survival were 30% and 20% longer, respectively, for patients with grade 2 glioma who received combination chemotherapy and radiation therapy compared with patients who received radiation therapy alone.

  - A trial, called the **Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx**, showing that women with estrogen receptor–positive early-stage breast cancer who have a low risk of recurrence based on a 21-gene expression assay can forgo chemotherapy and the associated side effects and be safely treated with hormone therapy alone.

- The **NCI Community Oncology Research Program (NCORP)** is a network of institutions that conducts research and clinical trials in community-based health care systems. Launched in 2014, NCORP is comprised of 46 community sites. Twelve of these sites focus on minority and underserved communities, including patients who live in rural areas and cannot travel far distances to receive treatment at an NCI-Designated Cancer Center. (Read more about one of these sites in the story about Chanita Hughes-Halbert, Ph.D., of the Medical University of South Carolina, on page 86.) NCORP participation accelerated the pace of enrollment in the NCI-MATCH trial and helped to reach traditionally underrepresented rural populations. NCORP builds on previous NCI programs to bring clinical trials and cancer care delivery research into the community, where most cancer patients—approximately 85%—are treated.



Providing Resources to Advance Research

NCI develops and maintains resources to help researchers prevent, diagnose, and treat cancer, including databases and specimen repositories, cancer-related tools, and other materials that are available to scientists and the public via NCI's website. The following represent just two of these kinds of resources.

- The **Surveillance, Epidemiology, and End Results (SEER) Program** facilitates the collection and analysis of cancer statistics at the population level. SEER serves as the authoritative source of information on cancer incidence and survival in the United States. The program oversees the only population-based cancer registries in the country that include a broad set of clinical elements, with the registries located at or associated with NCI-Designated Cancer Centers. NCI manages the program and collaborates with other organizations, including the American Cancer Society and the Centers for Disease Control and Prevention, to make SEER a success. Furthermore, SEER data are used extensively to support research beyond NCI, with 4,000 downloads of its public-use files annually. For example, researchers use SEER to track trends in cancer at the national, state, and local levels; understand

factors that influence these trends; and describe cancer disparities among different populations.

- The **NCI Natural Products Repository** holds more than 80,000 natural products obtained from all over the world and makes the products and their extracts available to academic and industry researchers. The products and extracts are screened for anticancer activity and used in the development of cancer drugs and for other medical uses. NCI's leadership role in natural products has increased as industry has begun to focus on screening synthetic (laboratory-made) chemicals, which are easier to analyze than the complex mixtures of chemicals present in natural products, which need to be fractionated further for study. To promote the use of natural products in this modern era of drug development, NCI is generating 1 million extracts for high-throughput cancer drug screening. As seen in the story on the development of eribulin mesylate on page 85, this unique resource harnesses the power of nature to identify and develop new drugs to treat and prevent cancer, which is fundamental to ensuring the health of many Americans.

Strengthening Small Business Innovation and Commercialization

NCI provides funding and support to drive the development and commercialization of novel technologies and products to prevent, detect, and treat cancer.

- NCI's **Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) Programs** are two of the largest sources of financing for early-stage technology in the United States. Small businesses are a national resource for technological innovation and a mainstay of the economy. These programs strengthen their role in federally supported research and development by providing funding, mentoring, and networking assistance to small businesses and researchers, like Avrum Spira, M.D., M.Sc., of Boston University. (Read about the lung cancer screening test Avrum developed on page 36.) NCI also helps connect researchers with government scientists who can help them develop promising cancer drugs, diagnostics, and devices. In addition, SBIR fosters participation by minority and socially disadvantaged companies in technology innovation.

- The **I-Corps™ at NIH** program, which is led by NCI in collaboration with the Centers for Disease Control and Prevention (CDC), supports training that will help project teams at NIH- and CDC-funded small businesses overcome key obstacles along the path of innovation and commercialization.

Conducting Research at NCI

Although the overwhelming majority of NCI's budget funds extramural research—that is, research conducted in laboratories and clinics throughout the United States—the national cancer research enterprise also includes work done by scientists at laboratories and offices located primarily on the National Institutes of Health (NIH) campus and surrounding locations in suburban Maryland.

Intramural Research Program

NCI's intramural research program (IRP) conducts long-term, high-risk research and clinical trials that would be more difficult for the extramural community or industry to complete. The IRP allows NCI to focus on emerging public health concerns and contributes to the training of the next generation of researchers in basic, clinical, translational, and epidemiologic research. IRP basic and clinical researchers at NIH's Mark O. Hatfield Clinical Research Center and Warren Grant Magnuson Clinical Center collaborate to provide compassionate patient care and unparalleled opportunities for advancing cancer research.

A few examples of IRP accomplishments include:

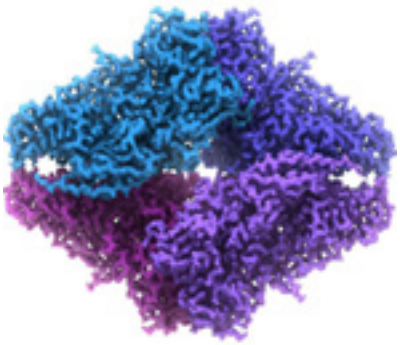
- Developing **treatments for rare tumors**, including the 2017 approval of avelumab (Bavencio®), the first drug approved by the Food and Drug Administration (FDA) for Merkel cell carcinoma, a rare but deadly skin cancer.
- Pioneering **adoptive cell transfer immunotherapy**, in which a patient's own cancer-fighting immune cells are extracted from their tumor, grown in large numbers in the laboratory, and then infused into the patient. This research has been applied in several clinical trials and is expected to be used more widely in the clinic in the next several years.
- Conducting basic scientific research on the human papillomavirus (HPV), which led to FDA-approved **HPV vaccines** and major advances in the prevention of cervical cancer and other cancers caused by HPV.
- Identifying **risks associated with tobacco use**, including the finding in 2016 that low-intensity smokers (those who smoked an average of less than one cigarette per day over their lifetimes) had an increased risk of early death, including death from lung cancer, compared with people who never smoked.
- Detecting risk-factor status for multiple types of cancer, including ***Helicobacter pylori* infection and gastric cancer**, discoveries that have led to the development of risk stratification models and clinical interventions to prevent or treat cancer.

Frederick National Laboratory for Cancer Research

The **Frederick National Laboratory for Cancer Research** is a government-owned, contractor-operated national laboratory that is dedicated exclusively to biomedical research. It is the Department of Health and Human Service's only federally funded research and development center. The Frederick National Lab offers unique partnering opportunities for academia, government, and the private sector to address the most difficult challenges in cancer prevention and treatment.

Major initiatives and partnerships of the Frederick National Lab include:

- The **RAS Initiative**, launched in 2013, which is exploring innovative approaches to attack the proteins produced by mutant forms of members of the *RAS* gene family.



A cryo-electron microscopy (cryo-EM) map of a protein created at the National Cryo-EM Facility hosted by the Frederick National Laboratory for Cancer Research

Credit: National Cancer Institute

The goal of the initiative is to develop effective therapies for *RAS*-related cancers. Because more than 30% of all human cancers—including 95% of pancreatic cancers and 45% of colorectal cancers—are driven by mutations in *RAS* genes, understanding the biology of RAS proteins is critical to finding better treatments for patients.

- The **Accelerating Therapeutics for Opportunities in Medicine (ATOM) Collaboration**, which is a partnership formed in 2017 by NCI, the Department of Energy, GlaxoSmithKline, and the University of California, San Francisco, to leverage their strengths in computational biology to dramatically accelerate the discovery and development of new cancer drugs.
- The **National Cryo-Electron Microscopy (cryo-EM) Facility**, which was opened at the Frederick National Lab in 2017, to capitalize on revolutionary changes in the cryo-EM field that allow researchers to capture exceptional imaging resolution at the near-atomic level. The facility is designed to meet the needs of cancer researchers who are engaged in structural biology cryo-EM research but do not have access to the latest technologies at their own institutions.

KEY TAKEAWAYS

- NCI leads programs to build, sustain, and diversify the cancer research workforce. This includes supporting the next generation of investigators, established researchers, and collaborative team science.
- NCI provides critical infrastructure that brings state-of-the-art cancer care and the benefits of clinical trials to more people.
- NCI conducts research and provides research resources that cannot or will not be provided by others.
- NCI advances the commercialization potential of scientific discoveries through support to small businesses.
- NCI supports unmet needs in cancer research through its intramural program and national laboratory.

FIGHTING CANCERS WITH A SEA SPONGE

In 2016, the Food and Drug Administration (FDA) approved the first drug that improved the survival of patients with liposarcoma—a drug made possible by a sea sponge. This drug, eribulin mesylate (commonly called eribulin or Halaven®), was also approved in 2010 for certain patients with breast cancer. The story of how a sea sponge led to a cancer drug spans three decades of NCI-supported research and collaboration among governments, a pharmaceutical company, and universities.

The medicinal properties of natural products, including plants and marine organisms, have long been a productive source of "lead" molecules for researchers developing cancer drugs. In fact, many cancer drugs are based on natural products, including paclitaxel (Taxol®) from the Pacific yew tree for breast and ovarian cancers and vinblastine (Velban®) and vincristine (Marqibo®) from another plant, the rosy periwinkle, for childhood leukemias and other cancers. In fact, a recent review of drug approvals has shown that 49% of all cancer drugs approved by FDA from around the 1940s to the end of 2014 were derived from natural products.

In 1986, Japanese researchers reported on a group of compounds called halichondrins, isolated from the sea sponge *Halichondria okadai*, that had promising anticancer activity. Subsequently, a team of NCI intramural and extramural investigators discovered that one of the halichondrins from this sponge and other sponge types from the Pacific blocked cell growth by inhibiting the protein tubulin, confirming its anticancer potential and demonstrating its mechanism of action. NCI worked with institutions in New Zealand to obtain a supply of this halichondrin for testing. Because it was present in such small amounts in the sponges, NCI-funded researchers, led by Yoshito Kishi, Ph.D., of Harvard University, developed a way to generate the halichondrin in the laboratory.

Recognizing halichondrin's potential against cancer, a pharmaceutical company licensed the compound and made a series of modified versions, or analogs, for testing. Positive results from the tests led to the development of one of the analogs, which became known as eribulin, in collaboration with NCI. NCI supported the preclinical studies and early clinical trials of eribulin, and the company subsequently tested the drug in large phase III clinical trials.

NCI's extensive work and investment, as well as the interplay of academia, industry, and government, played important roles in developing and bringing eribulin to market over the course of two decades. NCI-funded scientists demonstrated that eribulin was as efficacious as pure halicondrin and could be provided in more sufficient quantities. This persuaded a pharmaceutical company to continue its studies and development of eribulin and ultimately brought an effective therapy to cancer patients who had otherwise exhausted their treatment options.

CHANITA HUGHES-HALBERT, PH.D.

AT&T Distinguished Endowed Chair in Cancer Equity, Medical University of South Carolina

BRINGING RESEARCH TO THE COMMUNITY TO REDUCE DISPARITIES

Approximately 85% of cancer patients in the United States receive care in community settings, not at academic medical centers where most clinical trials take place. This is certainly true in South Carolina, where Hollings Cancer Center at the Medical University of South Carolina (MUSC) serves as the state's only NCI-Designated Cancer Center.

More than 30% of the people in South Carolina are minorities, and more than 40% live in rural areas. These individuals can often face logistical and financial challenges when trying to access clinical trials. For example, for someone who lives several hours from MUSC, receiving care there would take an entire day. "A lost day's work equals a lost day's pay" for many people in South Carolina, said Chanita Hughes-Halbert, a nationally recognized leader in cancer disparities research and behavioral science at MUSC.

Being able to join research studies in a person's own community allows them to miss less time at work, stay close to family and friends, and reduces the burden of participation in research while increasing the quality of their care. To enhance patient access to clinical trials and facilitate the participation of community providers in cancer research, NCI launched the NCI Community Oncology Research Program (NCORP) in 2014. Forty-six community sites comprise NCORP, each of which partners with other cancer care providers in their region.

Twelve of the NCORP sites are minority/underserved community sites that have

patient populations of at least 30% racial/ethnic minorities or rural residents. One of the minority/underserved sites is MUSC, which brought together community care organizations across the state as a result of its NCORP grant. Chanita leads the NCORP site along with public health researcher Marvella Ford, Ph.D., and hematologist/oncologist Carolyn Britten, M.D. The NCORP grant created a "team spirit" among the collaborating organizations and is facilitating interaction among researchers in different disciplines that traditionally are siloed, said Chanita.

Enhancing participation of patients in precision medicine trials is particularly important, Chanita said, because finding and subdividing patients into distinct groups based on the genomic characteristics of their tumors is "like looking for a needle in a haystack." She added, "A national effort is required to increase the pace of this research and for it to be successful."

As evidence of this, NCORP sites are playing a critical role in the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial, in which patients are assigned to receive treatment based on the genetic changes in their tumors. The number of patients in the trial increased from 3,000 to 6,000, thanks to increased resources provided by NCI's regular appropriation.

The trial reached its goal of sequencing the tumors of 6,000 patients in June 2017, nearly 2 years sooner than expected due to wide-scale adoption of the trial throughout NCORP and NCI's National Clinical Trials Network (NCTN). The unprecedented rate of patient enrollment was accomplished by more than 1,100 academic centers and community hospitals in all 50 states and Puerto Rico and is reaching traditionally underrepresented rural populations.

The MUSC NCORP grant is supporting enhanced access to clinical trials with a focus on minority and underserved communities with the goal of reducing cancer disparities. "Efforts to enroll more diverse patients helps ensure that we don't get to the end of trials and realize we won't be able to understand how treatments will work in different populations," concluded Chanita.

Professional Judgment Budget Proposal Fiscal Year 2019

(Dollars in millions)

FISCAL YEAR 2017 NCI BASE APPROPRIATION	$5,389	
TOTAL BUDGET INCREASE Proposed Allocation	$591†	$301 Inflation Adjustment* $45 Understanding the Mechanisms of Cancer $70 Preventing Cancer $40 Detecting & Diagnosing Cancer $70 Treating Cancer $25 Advancing Public Health in Cancer $20 Reducing Cancer Disparities $20 Training & Infrastructure
FY 2019 BUDGET REQUEST	$5,980	
	$400	FY 2019 CANCER MOONSHOSM FUNDING
FY 2019 GRAND TOTAL	$6,380	

* Adjustment includes inflation for the 2 years between FY 2017 and FY 2019.

† In addition to the inflation adjustment, the increase of $591 million includes $290 million (5.4%) for additional cancer research in seven priority areas.

plan.cancer.gov
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