Annual Plan & Budget Proposal for Fiscal Year 2022

At a Glance

DIRECTOR’S MESSAGE: MAINTAINING OUR FOCUS ON THE FUTURE

Decades of sustained investment in biomedical research have led to tremendous progress against cancer. This long-term commitment has driven our understanding of the biology of cancer and uncovered new approaches to prevention, screening, diagnosis, and treatment of cancer. Many of these discoveries have directly benefited biomedical fields well beyond cancer.

These strides were made possible by continued support from Congress, the dedication of scientists, the commitment of the cancer research advocacy community, and—from most importantly—the involvement of patients, survivors, and their loved ones.

We now know that cancer is not one, but thousands of different diseases. And yet, as much as we have learned, important gaps remain in our understanding of cancer.

I have personally witnessed the physical, emotional, and financial toll exacted by cancer. That toll has been compounded by the COVID-19 pandemic, in part because people with cancer may be at increased risk for complications from COVID-19. In addition, interruptions in health care services and concerns about exposure to the virus have led to delayed cancer screenings, diagnoses, and treatment. Early analyses suggest that these factors could result in thousands of additional cancer deaths in the years ahead.

NCI’s long history and expertise in navigating uncertainty and tackling the seemingly insurmountable leave us well positioned to confront today’s—and tomorrow’s—challenges. While
contributing our scientific expertise to the current public health crisis, we remain focused on our top priority: cancer research. We have taken steps to ensure that the cancer research engine continues operating—not simply to maintain the status quo, but to accelerate progress for the future.

Recent events have focused the world’s eyes on the continuing racial injustice in America. Inequity persists in cancer as well, as certain groups still face an increased risk of developing or dying from particular cancers. NCI has a long record of supporting research to better understand and overcome these cancer health disparities, and we are committed to continuing this crucial work.

We also must do more to increase diversity in the cancer research workforce to ensure that it reflects the diverse communities we serve. The perspectives and talents of populations underrepresented in the sciences are vitally important to the future growth of all areas of cancer research and care.

In recent years, NCI has seen a dramatic increase in new investigators entering the cancer field, as evidenced by a nearly 50% increase in grant applications submitted to NCI. Sustained budget increases across the cancer research continuum are critical to continue fueling excitement in the field and funding highly meritorious research proposals. It is NCI-funded investigator-initiated basic research that has served as the source of the most innovative and transformative work in cancer research, including work that has culminated in several Nobel Prizes in the last two decades.

As we approach the 50-year anniversary of the signing of the National Cancer Act of 1971, I’m reminded that the improvements we’ve seen in cancer care have been thanks to investments in basic science. Progress has been fueled by patients who have pushed for cures and scientists who have refused to give up. We cannot afford to turn away from promising research opportunities today, such as those laid out in this Annual Plan & Budget Proposal. With the nation’s support, nothing will stop us from advancing our understanding of cancer and reducing its burden—not just for some, but for all people.

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

KEY MESSAGES

• To pursue the immense opportunities across the cancer research continuum, investments are needed across a multitude of funding mechanisms. Capitalizing on these future opportunities will lessen the adverse effects of the COVID-19 pandemic on patients diagnosed with cancer.

• Strong congressional support led to a nearly 20% increase in NCI's budget from fiscal year (FY) 2013 to FY 2019. During this time, a dramatic increase in new investigators entered the cancer field resulting in a 50% increase in RO1 grant applications submitted to NCI. Continued infusion of funding into research project grants is necessary to capitalize on today’s scientific opportunities.

• The FY 2022 budget proposal will give NCI the ability to support grant commitments and further improve the payline for RO1 grants from the 10th to the 12th percentile. Doing so would allow NCI to fund a greater number of meritorious applications and make progress toward achieving the 15th percentile RO1 payline by FY 2025.

• With steady and sustained budget increases supporting a cadre of talented researchers, NCI will be able to support promising research opportunities that improve our understanding of cancer and reduce the burden of the disease.
SCIENTIFIC PRIORITIES

NCI drives advances in cancer by investing in a broad portfolio of research, from basic science to survivorship. In addition to investments in long-established areas of research, NCI pursues new and emerging scientific opportunities. The following areas represent just a few of the many areas that, with further investment, will catalyze progress in cancer research.

CANCER DRUG RESISTANCE

Drug resistance remains one of the biggest challenges in cancer therapy. Cancers often have multiple mechanisms for surviving and growing, which may differ from patient to patient, and even from tumor to tumor. Catalyzing research aimed at solving the puzzle of why cancers become resistant to treatment will enable development of new strategies to overcome or prevent drug resistance in patients.

MOLECULAR DIAGNOSTICS FOR CANCER TREATMENT

Precision medicine in cancer using genomic information about a patient’s tumor has revolutionized cancer diagnosis and treatment. Progress will continue as genomic and proteomic information are integrated, as doing so will provide a clearer picture of a patient’s cancer and help inform cancer treatment.

OBESITY & CANCER

Nearly 40% of adults and 20% of children are obese, and those percentages are growing. Not only is obesity associated with a higher risk of 13 types of cancer, it can also adversely affect cancer treatment and survival. Research to untangle the relationship between obesity and cancer will inform the development of effective strategies that prevent obesity and promote weight loss to reduce cancer risk and improve patient outcomes.

CANCER SURVIVORSHIP

The number of cancer survivors in the United States has grown dramatically over the past several decades, with more than 22.1 million estimated by 2030. More research is essential for developing effective interventions that mitigate the many short- and long-term adverse effects of cancer and its treatment. These interventions will improve the well-being and quality of life of cancer survivors.

NCI’S COVID-19 RESPONSE

CONTINUITY FOR PATIENTS AND RESEARCHERS

Although the COVID-19 pandemic has greatly disrupted daily life, NCI’s top priority is, and always will be, to advance cancer research and reduce the burden of cancer. NCI is taking steps to meet the needs of people with cancer and to keep the nation’s cancer research enterprise operating with as few disruptions as possible.

PRIORITIES FOR PEOPLE WITH CANCER

- Providing clear information about cancer and COVID-19
- Limiting disruptions to ongoing cancer clinical trials
- Providing care to trial participants while minimizing their risk of exposure

PRIORITIES FOR CANCER RESEARCHERS

- Supporting grantees whose work has been disrupted by the pandemic
- Extending funding application deadlines
- Quickly funding research on COVID-19 and cancer

CONTRIBUTIONS TO COVID-19 RESEARCH

NCI has unique resources and expertise to respond to the COVID-19 pandemic, including advanced technologies at the NCI-sponsored Frederick National Laboratory for Cancer Research and decades of support for research on the immune system and cancer and cancer-associated viruses. NCI has mobilized its nationwide research infrastructure to:

- Conduct studies of patients with cancer and COVID-19
- Develop and evaluate SARS-CoV-2 antibody tests and support research on serological sciences
- Search for and test compounds to treat patients with COVID-19

“NCI has tremendous expertise and unique research capabilities that make our participation in the response to this pandemic a moral obligation.”

—NCI Director Dr. Norman E. Sharpless
This budget proposal for fiscal year (FY) 2022 includes investments in critical research to advance progress in understanding and treating cancer as well as support for the infrastructure and training that enables cutting-edge research to succeed.

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

Investments in investigator-initiated research supported through research project grants (RPGs), including R01 grants, are the source of some of the most innovative ideas in cancer research.

The FY 2020 budget increase allowed NCI to further invest in RPGs by restoring noncompeting grants to 100% of their committed levels and increasing R01 paylines by 25% compared with the FY 2019 level. The FY 2022 budget proposal will allow NCI to sustain recent growth in RPGs and to further improve the payline for R01 grants from the 10th to the 12th percentile—and will get the institute closer to achieving the 15th percentile payline by FY 2025.

Additional key investments include training the next generation of cancer researchers and supporting the NCI-Designated Cancer Centers and practice-changing clinical trials programs, which enroll patients in clinical trials at more than 2,500 academic and community sites across the country.
The Hidden Drain of Cancer: Long-Term and Psychosocial Effects

In 2013, then 5-year-old Phineas received CAR T-cell therapy for acute lymphoblastic leukemia (ALL) through an NCI clinical trial. His dad Carlos shared how Phineas has been faring since doctors declared him cancer-free in 2013 and how the family coped with his cancer and its treatment.

On his way back to the NIH Clinical Center to be with his son Phineas, Carlos got his first speeding ticket in 8 years. Hours before, he had left his teenage daughter with neighbors so he could be with Phineas. In Virginia, state police had pulled him over on I-95 as he urgently returned to NIH in Maryland. He paid the ticket.

His daughter had just started school after summer break. Carlos didn’t want her to miss classes, so he left her with neighbors for a few weeks. Several states away from home, 5-year-old Phineas had received his CAR T-cell transfusion 3 days earlier and was spiking an alarmingly high fever and had become nonresponsive. When Carlos finally made it to the NIH Clinical Center that night, he found his wife with Phineas, exhausted.

Phineas pulled through, and ultimately, the treatments for his cancer were successful. Now 12 years old, he spends his summer days as many kids his age do: playing on the computer, swimming in the local lake, and hiking trails.

Six years before Phineas was diagnosed with ALL, Carlos and his wife had lost an 18-month-old daughter to acute myeloid leukemia (AML). Despite ALL and AML both being blood cancers, they are very different diseases, and there were very few treatment options for AML at the time.

“The first time around, you can lean on your ignorance of the process. The shock carries you through,” Carlos recalled from the experience with his daughter. “Learning Phineas had cancer was tough. As awful as cancer is, we were actually a bit jubilant when we heard Phineas had ALL. We already knew it was supposed to be the most curable type of cancer a kid could get.”

An Experimental Treatment: CAR T-Cell Therapy

Carlos and his wife figured Phineas was facing 3 years of discomfort from chemotherapy and other cancer-related treatments. They watched for 4 months as Phineas suffered metabolic issues in response to various chemotherapy drugs. His liver did not clear the drugs out of his system quickly. His cancer did not respond.

In 2013, CAR T-cell therapy was experimental—a promising treatment that came with many uncertainties.
Phineas’s parents were aware that some children who have CAR T-cell therapy experience spectacular remissions followed by tragic relapses. “We knew this was not a sure thing,” Carlos said. “We wanted to give it a shot, though, before going down the road of just dumping more chemotherapy into this kid.”

Only a few cancer centers offered this new experimental therapy, and they had wait lists. Carlos discovered an NCI pediatric clinical trial testing CAR T cells engineered to target a protein called CD19. Phineas enrolled and received his CAR T-cell transfusion in September 2013. His doctors declared his cancer to be in complete remission 28 days later.

Today, a handful of CAR T-cell therapies have been approved by the Food and Drug Administration to treat a number of cancers.

**Seven Years Cancer-Free**

Being a 7-year cancer survivor doesn’t slow Phineas down. He has transitioned to seeing a primary care doctor, as opposed to an oncologist, and participates in a yearly cancer survivorship clinic. Despite missing first grade and spending a year in Costa Rica with his family, Phineas recently finished 5th grade as a top student.

His parents worked hard to make Phineas’s childhood as normal as possible. “His childhood was spent in hospitals,” Carlos reflected. “We tried to make it a really weird science-themed summer camp the whole time.” They always tried to see the positive in what was happening and to have a good time. For example, the nurses were willing participants in the practical jokes they played and laughed when they flew an inflatable blimp by remote control down hospital corridors.

**A Need to Identify the Long-Term Effects of CAR T-Cell Therapy**

Carlos is not concerned about any lingering cognitive effects from his son’s cancer treatments. He and his wife do continue to watch for physical effects, such as extra bone growth and other known late effects from radiation. They are glad that doctors have identified the severe long-term physical consequences of radiation and chemotherapy. However, late effects of CAR T-cell therapy have not been fully identified by scientists.

Carlos shared Phineas’s ordeal and his family’s experience at an NCI conference in May 2020 that brought together immunologists and other researchers to consider how to help patients and families with longer-term toxicities and psychosocial effects from CAR T-cell therapy. The emotional rollercoaster that the family has been on for more than a decade may have come to a stop, but the occasional cracks in Carlos’s voice and pauses as he tells their story reflect the lasting impact of the family’s experience and the continued need for emotional recovery.

Carlos expressed his family’s appreciation for the research that made a treatment possible for Phineas and the NIH Clinical Center where he received it: “Thank you for everything you are doing and keep on ‘sciencing’!”

**Posted: August 31, 2020**
Treating a Rare Genetic Syndrome to Prevent Cancer

Maria watched with dismay in the spring of 2020 as COVID-19 sent the nation and the world reeling. “Physical distancing” and “rigorous hygiene practices” were trending phrases that Maria was already well acquainted with.

A Medical Mystery

A decade and a half prior, a medical exam that was required for Maria’s application to join the Peace Corps raised a flag. It revealed a very low white blood cell count. She was stunned, as she had always felt healthy and had played soccer, run track, and competed in triathlons in high school and college.

For the next 10 years, Maria ran the gauntlet of medical tests and saw numerous physicians at five large hospitals without receiving a clear answer to explain the low white blood cell count. During this time, she was experiencing gynecological pain, and her doctors eventually found precancerous lesions and recommended surgery. And she still had not been given an explanation for her low white blood cell count.

Eventually one of her doctors connected Maria with Steve Holland, M.D., at the National Institute of Allergy and Infectious Diseases (NIAID). In late December 2016, she talked with his team about her precancerous lesions and other medical history, and they thought they could help her. She arrived at the NIH Clinical Center 6 weeks later for a thorough examination to determine if she had a rare condition that would make her eligible for a clinical trial.

Leukemia Prevented with a Bone Marrow Transplant

Test results identified a deficiency in a gene called GATA2. Research had shown that sporadic gene mutations on one copy of the GATA2 gene can lead to a syndrome called MonoMAC, which is characterized by a compromised immune system leading to debilitating infections and, often, progression to leukemia. Dennis Hickstein, M.D., a senior investigator in NCI’s Immune Deficiency Cellular Therapy Program, was conducting a trial to address MonoMAC syndrome, and Maria agreed to participate in it.

In the fall of 2017, Maria underwent chemotherapy followed by a bone marrow transplant. “The transplant saved Maria’s life,” Dr. Hickstein said. “There’s a 90% survival rate in this disease when it’s treated.” He noted that about half the people with MonoMAC progress to leukemia. The key to helping Maria was identifying the GATA2 mutation and making the MonoMAC syndrome diagnosis, something that had eluded her doctors for more than a decade.

Maria is extremely grateful for her opportunity to participate in Dr. Hickstein’s clinical trial and attributes the transplant to preventing her from developing leukemia. “I saw the impact of science firsthand. I watched the
lesions melt away over a 6-week period.”

Until her new immune system kicked in following the transplant, however, Maria was very susceptible to infections. She spent 3 months in isolation in and near the NIH Clinical Center to ensure that she did not come into contact with infectious agents—viruses, bacteria, and fungi—and, once released from isolation, she continued taking antifungal medicines as a precaution. Also, anything she touched was sanitized: purse, wallet, phone, keys, doorknobs, steering wheel, and other surfaces.

In March 2020, to help fellow Americans struggling with isolation and fear of COVID-19, she drew from her experiences and shared her successful practices in remaining virus-free in an online article. “I had no immune system for months after my bone marrow transplant,” she wrote. “Here’s how I avoided viral illness, and how you can, too. It’s easier than you think.”

**Posted:** August 31, 2020
Having Faith in Science to Treat Prostate Cancer

As a pastor and leader in the Black community, Bill has devoted his life and career to working in the service of others. And he has great faith in the goodness of people. Nineteen years ago, he was led to start a new church to provide physical and spiritual solace to members of the community. He used his influence to help Washington, DC, administrators bring local leaders of many faiths together to help improve conditions for residents.

Five years ago, Bill was diagnosed with aggressive prostate cancer and took his own leap of faith and enrolled in a first-in-human clinical trial for a new prostate cancer treatment approach.

When Bill visited his doctor in early 2015, a blood test revealed an elevated prostate-specific antigen (PSA). PSA is a protein produced by cells of the prostate gland. While doctors consider a normal PSA level to be in a range from 0–4, the level can be higher. Doctors pay attention to elevated PSA levels as they may indicate possible prostate cancer. Bill’s PSA was in the 30s and, after further screening, he learned that he had advanced-stage prostate cancer. Removal of his prostate reduced his PSA level, and it was kept low temporarily with radiation treatments until his PSA level catapulted into the high 60s.

First Patient to Join a Novel Combination Therapy Trial

Bill discussed next steps with his physician and learned about a phase 1 clinical trial led by James Gulley, M.D., Ph.D., chief of the Genitourinary Malignancies Branch in NCI’s Center for Cancer Research. The goal of the trial was to determine the safety of the experimental immunotherapy PROSTVAC in combination with the Food and Drug Administration-approved immunotherapy nivolumab (Opdivo) for men whose prostate cancer had progressed despite receiving other therapies. Immunotherapies have been largely ineffective against prostate cancer to date, but scientists believe combining agents may provide an approach for overcoming drug resistance and improving antitumor immunity.

Bill was the first patient to be enrolled in the phase 1 trial. From the start, his cancer responded well to the combination therapy. His PSA level plummeted in 3 months, from a high of 67 to less than 9. Bill was elated. His greatest discomfort was some swelling in his ankles, which went away when he elevated his feet. A phase 2 trial is underway to determine if additional patients with prostate cancer will be helped by this combination therapy.

Bill continues to help the community by delivering physical and spiritual comfort to his parishioners and those in need. He blesses the day he found the NCI clinical trial and is determined to raise awareness about how
science can help people.

“I’m a living witness that the benefit of research is well worth the cost,” Bill avowed. “Now I’m going to be able to continue doing what I do: to help thousands of people on a monthly basis. And I definitely want to help my fellow Black men take better care of their health.”

Posted: August 31, 2020
Removing a Protective Coat from Prostate Cancer

Jelani Zarif, Ph.D., had a very early interest in life sciences, which his family encouraged. He was only 17 when he saw the practical side of the medical field by completing a nursing assistant certification program and helping to care for nursing home residents.

Jelani chose a career path in research to find better evidence to guide medical care. As an undergraduate student, he studied the effects of crude extracts from a Nigerian basil on prostate cancer cell proliferation. Research internships, graduate school, and two postdoctoral fellowships fed his interest in how to harness the body’s immune system to stop and eliminate prostate cancer.

As a postdoctoral fellow, Jelani applied for the NCI Transition Career Development (K22) Award, and within a year of joining Johns Hopkins University as an assistant professor, he received the award from NCI. The NCI K22 award supports investigators as they transition to independent academic faculty positions. Jelani had learned about specific NCI training awards and research grants when he visited NCI a few years earlier. He was thrilled when he received notice about his award and celebrated at a dinner with colleagues.

Macrophages: Metastasis-Supportive Factors for Prostate Cancer

Prostate cancer treatments may initially work for patients. However, after a few years, a majority of prostate cancers stop responding to these therapies, and the cancer spreads, or metastasizes. Jelani’s vision is to find novel therapeutic targets to benefit men with lethal prostate cancer and attenuate metastasis. To do this, his NCI-supported studies focus on macrophages, immune cells that tumors can commandeer to circumvent therapies. Macrophages do this by providing the tumor with factors that support metastasis and suppress an immune response.

Jelani premises his research on the idea that if tumor-promoting macrophages no longer infiltrated tumors, then the cells from the adaptive immune system (such as CD4+ T cells) could better infiltrate the tumor microenvironment and destroy the tumor. Using animal models and prostate cancer tumor models, Jelani and his colleagues are investigating whether tumor-associated macrophages can be persuaded not to provide pro-metastatic factors for the tumor. He is trying to do this by altering how the macrophages take up an amino acid called glutamine.

“The tumor-associated macrophages are responsible for increasing the metastatic potential of the tumors,” Jelani explained. “If we target them, maybe we can impede metastasis and the tumors will respond better to therapy.”
Jelani’s hope is that his NCI-supported research will help scientists understand why conventional therapies eventually fail and why immunotherapies work for a minority of patients with prostate cancer. He hopes that, within 10 years, effective regimens and treatment methods will be available for all patients who present with lethal forms of prostate cancer or whose cancer becomes metastatic.

**Skills for a Career in Science Research**

Jelani knows that he developed a solid set of skills early in life that helped him in his research career. He also participated in science fairs and an after-school science academy in elementary and high school. His mother enrolled him in karate in second grade, and he played trumpet throughout grade school, high school, and college. “Both karate and trumpet playing required assiduous practice, balance, and discipline,” he reflected. “I carried those qualities right into the lab.”

Jelani mentors college-bound students, particularly those who have an interest in science. He encourages them and his laboratory staff to work smart, work hard, read the literature, and always have publication-ready data available. Those are some of the things, he notes, that can help them be better prepared for a career in cancer research.

**Posted:** August 31, 2020
Helping Cancer Survivors Eat Better and Exercise More

It’s common wisdom that good nutrition and exercise are keystones for good health, and they are particularly important for cancer survivors, who face the risk of cancer recurrence among other health concerns. Wendy Demark-Wahnefried, Ph.D., R.D., works every day to help cancer survivors improve their lives through better nutrition and more physical activity. She practices what she preaches. She loves cooking tasty, healthy meals, and she enjoys ballroom dancing with her husband—the foxtrot and rumba are among her favorite dances.

A Detroit native and the first female in her family to graduate from college, Wendy obtained degrees in Michigan and New York in nutrition science and conducted cancer research in North Carolina and Texas before being recruited to the University of Alabama at Birmingham. Her research career has covered basic, clinical, and behavioral sciences, including studying how molecules in our food can affect cancer growth; nutrition-related concerns of cancer patients; and effective lifestyle interventions that improve the overall health of cancer survivors, particularly minority and rural populations.

AMPLIFYing Ways to Improve Cancer Survivor Health

Wendy currently leads the NCI-funded project AMPLIFY, which stands for Adapting MultiPLe behavior Interventions that eFfectivelY Improve Cancer Survivor Health. AMPLIFY is a web-based diet and exercise intervention designed to help participants lose an average of one pound per week. Emphasis is placed on adopting healthy dietary behaviors and increasing physical activity to lose body fat while preserving muscle. Long-term behavior change is the ultimate goal. “I’m interested in durable changes,” Wendy emphasized, “in which patients develop and maintain good habits, over multiple years.”

Alabama is an important place for Wendy’s work. With approximately three of every four residents considered overweight or obese, the state was ranked sixth in the nation for rates of adult obesity in 2020. It is also home to very large rural and African-American populations, which provide an opportunity for the intervention, if successful, to help reduce existing disparities. “The health disparities in Alabama are so great,” she said. “There’s so much to do that the opportunity to work here grabbed me.”

“I think of our work as ‘bench-to-trench,’” she explained. Her interdisciplinary team includes clinical psychologists, exercise and nutrition scientists, physicians, biostatisticians, and health economists. In designing AMPLIFY, Wendy drew on findings from her earlier NCI-funded research aimed at helping breast, prostate, and
colorectal cancer survivors make behavioral changes that improve their quality of life and reduce the risk of cancer recurrence. Among these findings, women with breast cancer benefit from resistance training exercises, and cancer patients who receive counseling via telephone and mail, rather than in person, can become more active and achieve their weight management goals.

Wendy and her team designed AMPLIFY to be a scalable intervention. Organizations like the American Cancer Society, American Society of Clinical Oncology, hospitals, and large health systems were brought into the planning process early, so they could provide input into how the intervention should be designed to best help minority and rural populations facing health disparities.

AMPLIFY was set to begin in the spring of 2020, with more than 100 people already enrolled in the research study, including almost 40 minority participants. The launch was delayed because of the COVID-19 pandemic, but beta-testing has already yielded promising results.

“I learned how to watch my caloric intake and what foods to avoid,” said one beta-tester. “By following the study’s instructions and suggestions, I lost the desired pounds and more. Right now, I feel great!”

Wendy and her team are finding ways to collect data safely during the pandemic and continue to advance their research in the face of these major challenges. Wendy hopes that AMPLIFY will expand in the future to help adolescent and childhood cancer survivors as well.

**Posted:** August 31, 2020
Cancer Drug Resistance: Unraveling Its Complexity

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• Treating Cancers Like Evolving Ecosystems
• Degrading—Not Blocking—the Target to Avoid Resistance
• Using Advanced Preclinical Models to Address Resistance

It’s a heartbreaking story, and one that happens too often. A patient with advanced cancer receives a drug that helps shrink their tumors, allowing them more time with family, but then weeks or months later the cancer comes back and the drug no longer works.

Drug resistance remains one of the biggest challenges in cancer therapy. It exists across all types of cancer and all modes of treatment, including molecularly targeted therapy, immunotherapy, and chemotherapy. Solving the puzzle of why cancers become resistant to therapy and how to overcome or prevent it is a goal that NCI is pursuing on many fronts, including basic science to understand biological mechanisms and clinical trials testing new treatment strategies.

Multiple factors, within cancer cells themselves and in the local environment in which the cancer cells exist (the tumor microenvironment), contribute to how well a drug works. These factors may differ from patient to patient and even among tumors in a single patient. Tumors are made of diverse cells that may have different genetic, epigenetic, and metabolic characteristics that have different sensitivities to treatment. Tumors also consist of immune cells, blood vessels, fibroblasts, and other cells and components that interact with the cancer cells. These interactions often promote tumor development, progression, and response to treatment.

Although a drug may kill some cancer cells, almost invariably a subset of them will be resistant and survive the treatment. Cancers often have multiple mechanisms for surviving and growing, which may change over time and in response to treatment. That is why combining treatments that have different mechanisms of action can kill more cancer cells and reduce the chance that drug resistance will emerge.

Most of the research on drug resistance has focused on identifying genetic mechanisms, such as mutations that alter a protein such that it impairs the binding of a drug. Research is revealing the importance of additional mechanisms of drug resistance, such as epigenetic factors that regulate the activity of genes and the dynamics between diverse cells in the tumor microenvironment. Overcoming resistance, then, requires understanding these complex biological processes in the first place, to better anticipate and steer the dynamic, multidimensional evolutionary process unfolding inside a patient with cancer.

Aided by advanced preclinical tools and new drug design approaches, NCI-funded researchers are revealing a clearer picture of cancer drug resistance and developing new treatment approaches to overcome it.
Targeting Cancer Cell Plasticity

Starting in 2006, doctors began to describe rare cases of patients with non-small cell lung cancer (NSCLC) whose cancers transformed into small cell lung cancer after treatment with EGFR inhibitors. This change in cell identity is one type of what scientists refer to as cell plasticity, and NCI-funded research is piecing together the puzzle of how it may hinder cancer treatment.

Cell plasticity is a cell’s ability to undergo changes that alter its appearance and function (its phenotype). These changes can occur in cancer cells because of genetic and nongenetic alterations, cues from other cells in the tumor microenvironment, and/or drug treatment. A cell’s ability to change and adapt offers it additional routes to resist treatment.

More recently, similar observations emerged from men with prostate cancer who were treated with androgen deprivation therapy: aggressive and deadly forms of neuroendocrine prostate cancers emerged. In addition to NSCLC and prostate cancer, scientists have described cell plasticity in several additional cancer types, including melanoma and breast cancer.
While different cancers demonstrate their own patterns of cell plasticity, NCI-funded research has revealed some biological mechanisms that are common across cancer types. For example, research supported by NCI has implicated EZH2, an enzyme that regulates gene expression, in the ability of both NSCLC and prostate cancer to change phenotypes. Thus, research on one cancer may enrich studies of resistance patterns in other cancers, resulting in the identification of treatments that could work for several cancer types. This example illustrates that our understanding of the fundamental and molecular mechanisms of cancer is fueling advances in precision oncology, including drugs approved to treat cancers with specific genetic abnormalities rather than where in the body the cancer started.

**Treating Cancers Like Evolving Ecosystems**

A tumor can be thought of as an ecological system that evolves over time. Researchers are therefore applying the concepts of evolutionary ecology to study cancer and its response to treatment. Evolutionary ecology is a scientific field that examines how interactions among species and between species and their environment shape species through selection and adaptation, and the consequences of the resulting evolutionary change.

As an example, NCI-funded research led by investigators at Cleveland Clinic and Case Comprehensive Cancer Center recently developed an "evolutionary game assay" that directly quantifies and describes the interactions between tumor cells that are sensitive and resistant to a targeted therapy in an experimental model of NSCLC. They found that the interactions between cells were different under different conditions. The researchers suggest that changing the types of interactions between cells—in other words, the "games they play"—can co-opt the cells’ evolution to better help the patient by preventing drug-resistant cells from “winning.”

Other NCI-funded studies are testing whether different drug doses and schedules might decrease the likelihood that drug resistance will develop as a result of evolutionary dynamics. For example, if drugs can be given in a way that allows a proportion of the easier-to-treat sensitive cells to disproportionately survive, they may compete with and block the growth of the resistant cells in the tumor. With this adaptive cancer therapy approach, it is possible that the tumor may never be completely eradicated, but it may remain relatively stable, thereby limiting the development of uncontrollable drug resistance.
Degrading—Not Blocking—the Target to Avoid Resistance

Using new technology to degrade proteins of interest, such as those that drive cancer cell growth, is an emerging cancer treatment strategy. One example of this technology is called proteolysis targeting chimera (PROTAC), in which molecules are generated that tag a specific protein for degradation by a cell’s normal machinery for getting rid of unwanted or damaged proteins. An advantage of this approach is that it can avoid some mechanisms of drug resistance seen with some cancer therapies, such as mutations in the target of a drug or overexpression of the target.

For example, NCI-funded researchers at Yale University created a PROTAC molecule as a potential treatment for advanced prostate cancer. Androgen receptor (AR) signaling plays a pivotal role in prostate cancer initiation and growth, and drugs that inhibit ARs are the standard of care for patients with metastatic disease. Unfortunately, most tumors treated with AR inhibitors eventually develop drug resistance. Some mechanisms of resistance result in continued AR signaling despite the presence of these drugs.

The PROTAC molecule the Yale team invented consists of an AR-targeting portion and a portion that binds selectively to a protein, called E3 ligase. The E3 ligase is part of the cell’s normal machinery that degrades proteins. With additional support from NCI’s Small Business Innovation Research (SBIR) program, Arvinas, Inc. of New Haven, Connecticut, is further developing and testing this PROTAC in clinical trials for patients with metastatic prostate cancer whose cancer has progressed after AR therapy.
HOW PROTACS USE OUR CELLS’ NATURAL DISPOSAL SYSTEM TO KILL CANCER-CAUSING PROTEINS

An emerging cancer treatment strategy supported by NCI uses new technology to degrade proteins that drive cancer cell growth. One example is proteolysis targeting chimera (PROTAC) technology, in which molecules are generated that tag a specific protein for degradation by a cell’s normal machinery.

WHAT OUR CELLS DO NORMALLY

Human cells have a mechanism to dispose of proteins when they become misfolded, mutated, or are no longer needed.

1. E3 ubiquitin ligases are molecules that act like the ‘garbage police’ in a cell, always looking for proteins that need to go.

2. The ligases tag proteins with a ubiquitin molecule, labeling the proteins for destruction. A ‘ticket from the garbage police.’

3. When the protein gets enough tickets, or a chain of tags, the protein is directed to the proteasome, which acts like the ‘garbage truck’ of the cell that picks up and disposes of the marked proteins.

SOME ABNORMAL PROTEINS CAUSE CANCER

Abnormal proteins can contribute to the uncontrolled growth of cells, leading to cancer.

What if we could send cancer-causing proteins to the garbage bin?

PROTAC HARNESSES THIS NORMAL PROCESS TO DEGRADE CANCER-CAUSING PROTEINS

A PROTAC is a small-molecule drug with two binding regions.

1. One end binds specifically with a cancer-causing protein.

2. The other end of the PROTAC molecule binds with the E3 ligase (‘garbage police’) and starts tagging, or issuing tickets to, the cancer-causing protein.

3. The PROTAC molecule takes advantage of a normal process that already exists to direct the cancer-causing protein to the proteasome (‘garbage truck’) for disposal.
Using Advanced Preclinical Models to Address Resistance

Researchers have traditionally used cancer cell lines to study mutations and other mechanisms that make cancer cells sensitive or resistant to therapies. But cell lines do not always share key features of cancers found in patients. In addition, cancer cell lines lack the three-dimensional structure of a tumor found in a person and the relationships with surrounding cells in the tumor microenvironment.

Animal models, such as mice that carry tumors implanted from a sample of a patient’s cancer, can more closely resemble the tumors found in humans. The tumor microenvironment and cancer growth, progression, and treatment effects of animal models more closely mimic those found in people. However, animal models are expensive, can take months to produce, and are not made in large enough quantities for testing more than a few drugs at a time. They also lack an intact immune system, making them inadequate to study the interaction between the immune system and cancer. While current cancer models are useful for answering some research questions, additional tools are needed.

NCI-funded researchers are leveraging new technologies and models to gain a fuller understanding of drug resistance. They include three-dimensional human tumor cultures and engineered platforms that support living human tissues, both of which incorporate cells that surround and interact with tumor cells in the tumor microenvironment to mimic conditions in the human body.

Miniature tumors called patient-derived tumor organoids are three-dimensional cancer cell clusters grown in the lab from a sample of a patient’s tumor. Scientists are using them in the laboratory to study various aspects of cancer biology, including mechanisms of drug resistance. Researchers have developed organoids from a variety of cancer types, including breast, prostate, liver, brain, and pancreatic cancer.

One example of this research is in pancreatic cancer, which is one of the most lethal cancer types, in part because it is largely resistant to treatment and is generally detected at a late stage after the cancer has spread. NCI-funded researchers at Cold Spring Harbor Laboratory in New York and their collaborators have created a “living library” of pancreatic cancer organoids derived from patient samples from multiple clinical institutions. In a retrospective analysis of a small number of patients, the organoid’s sensitivity to chemotherapy reflected the patient’s response to therapy. In addition, tumor sampling in a single patient over time predicted the development of chemotherapy resistance that paralleled disease progression in the patient. Understanding why resistance emerges and having models to help predict it could improve the selection of treatments for patients in the future.

Scientists are developing additional cancer models that accurately represent the structure and function of tumors in human organs and tissues. For example, tissue chips are three-dimensional cross sections of living human tissue on a device about the size of a computer memory stick. For cancer researchers, tissue chips and other engineered tumor systems are enhancing the understanding of tumor physiology and aiding cancer treatment research.

For example, NCI is funding research projects that are developing and using engineered tumor systems to study drug response and resistance in cancers of the brain, ovaries, and breast. In addition, NCI’s SBIR program has supported several companies developing cancer chips, including one developed by researchers at the University of Virginia and HemoShear Therapeutics, LLC of Charlottesville, Virginia, to assess drug sensitivity and resistance in pancreatic cancer.
Molecular Diagnostics for Cancer Treatment: Expanding beyond the Genome

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• Bolstering Proteomic Research through Collaboration and Data Sharing
• Moving New Proteogenomic Diagnostic Approaches into the Clinic

NCI’s investments in cancer genomics research have transformed our understanding of cancer, advanced the conduct of clinical trials testing the efficacy of cancer therapies, and changed the way oncologists select treatments for patients. These investments have produced valuable resources such as The Cancer Genome Atlas (TCGA), a publicly available catalog of cancer genome information covering more than 30 cancer types.

The genome codes for proteins that carry out functions in cells—both normal and tumor cells. Mutations in specific genes that affect how the resulting proteins function, can contribute to the development and progression of cancer.

Aided by this knowledge and advances in genomic sequencing technology, oncologists are increasingly selecting therapies based on the specific genomic abnormalities identified in a patient’s tumor. This genomic information often comes from a molecular diagnostic test.

Molecular diagnostic tests detect specific biologic molecules, or biomarkers, in a patient’s tissue and fluid samples. Molecular diagnostic tests can be used to select a cancer therapy and/or to monitor the effects of a treatment based on characteristics of or changes in the biomarker.

This approach has revolutionized cancer diagnosis and treatment. However, many patients who are matched to a therapy based on the genomic profile of their tumors either do not respond to the therapy initially or do not experience a sustained response.

That may be, in part, because key information about the biology of the tumor is missing from looking at the genome alone. While the presence of mutations can be determined from sequencing a tumor’s genome, the effect of mutations on protein function cannot be fully understood without interrogating the proteome, including the many modifications that occur to proteins in a tumor. Changes that normally occur in proteins after they are made (post-translational modifications) can affect how proteins function or how long they are present in a cell.

The proteome is the entire complement of proteins that is or can be expressed by a cell, tissue, or organism. Cancer proteomics is the comprehensive characterization and quantification of the proteome of cancer cells.
A better understanding of cancer at the protein level will enhance cancer diagnosis and treatment by providing more details about what is happening in tumors. Furthermore, proteogenomics, the integration of proteomics with genomics, produces a clearer picture of a tumor’s biology and will enable the development of new molecular diagnostic tests. Yet, developing protein-based biomarkers for cancer treatment has been hampered, in part, by the technical challenges of working with proteins, which are more complex than nucleic acids (DNA and RNA).

NCI supports several large initiatives in cancer proteomics to overcome these challenges and pave the way for the next generation of molecular diagnostics for cancer. NCI has been supporting cancer proteomics at multiple levels across the research continuum, from the development and validation of methods for protein identification and quantification, to the basic research needed to better understand the cancer proteome, to the integration of proteomic assays, to applying the information uncovered in clinical trials and patient care.

With sustained investments in proteogenomics research, doctors will, in the future, be able to assemble a more complete picture of a patient’s tumor—one that informs diagnosis and treatment and improves outcomes.
Bolstering Proteomic Research through Collaboration and Data Sharing

The NCI-supported Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a collaborative effort among academic institutions, industry, and several federal agencies to measure, in a rapid and large-scale manner, the entire complement of proteins in tumors and combine this information with genomic, imaging, and clinical data from patients. Efforts by the consortium have produced standardized methods for proteomics research; revealed new aspects of tumor biology that were not evident from genomic information alone; and identified additional targets for cancer treatment.
So far, proteogenomic characterizations have been completed for 11 tumor types, with four more anticipated in 2021. All the information assembled by CPTAC is made publicly available so that others can use it to make their own discoveries. With these data, NCI has developed some of the world’s largest public, open-access repositories of data. These repositories include DNA, RNA, protein, and imaging data on many cancer types, and the list of cancer types is growing. These data “live” in the NCI Cancer Research Data Commons, a virtual platform for secure data storage and sharing. The Proteomic Data Commons went live in 2020, joining the Genomic Data Commons, and the Imaging Data Commons is anticipated to be available soon.

NCI and the Departments of Defense and Veterans Affairs have partnered to advance the clinical utility of proteogenomics. The tri-agency Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) network aims to incorporate proteomic and genomic analyses into patient care to identify targets for therapy and better predict how patients will respond to therapy.

**Moving New Proteogenomic Diagnostic Approaches into the Clinic**

Many challenges exist in translating a potential biomarker identified in the laboratory to one that can be used in the clinic. Combining multiple biomarkers, including genomic and proteomic information, adds more complexity and introduces additional hurdles to overcome.

NCI is supporting research through CPTAC and other initiatives to advance the identification and use of protein molecular markers and proteogenomic information for clinical purposes. For example, NCI-funded Proteogenomic Translational Research Centers are using samples previously collected from patients who participated in clinical trials to see if biomarkers derived from proteogenomic information can predict the outcomes observed at the end of the trials. If these biomarkers can accurately predict patient outcomes, they potentially could be used to design the next generation of prospective studies and new clinical trials to further test the biomarkers’ utility.

Understanding proteins—their expression, modifications, and abnormal functions in cancer development and progression—is critically important when developing drugs, selecting treatments, and predicting treatment response. Integration of proteomic information is the next step in precision oncology.

**Aiding Drug Development**

A pharmacodynamic (PD) marker is a measurable indicator of a drug’s effect on its target in the body. For example, blood glucose levels are a PD marker of the effect of insulin. PD biomarkers provide critical information about whether a drug is hitting its intended target and having its intended biological effect; thereby providing insights about the dose and timing of drug delivery. This type of information is important in drug development.

NCI-funded researchers at Fred Hutchinson Cancer Research Center and their industry collaborators applied a cutting-edge proteomic technology for the first time to guide the selection of a PD biomarker that could be used in patients. Using primary human cells and patient-derived models, they identified a protein-based biomarker that reflected the effect of an investigational drug that targets the ATM protein. ATM is an important protein in signaling DNA damage in a cell.

Further investigation showed that the biomarker was a useful indicator of the inhibition of a second protein
called ATR. ATR works in concert with ATM to alert a cell that DNA damage has occurred. The investigators then developed a test intended for clinical use to measure this biomarker in patient samples in future phase 2 clinical studies testing drugs that inhibit ATM and ATR. A PD marker of this kind would greatly speed the development of these types of drugs for the treatment of cancer.

Selecting Treatment

The NCI-MATCH trial and NCI-COG Pediatric MATCH trial use genomic characterization of a patient’s tumor to match a targeted therapy to the patient based on a mutation in the tumor’s DNA. Proteogenomic characterization will enhance this concept to include protein characterization and treatment selection based on protein level, activation, or modification.

Recently, NCI-funded researchers from Baylor College of Medicine, the Pacific Northwest National Laboratory, and their colleagues performed proteogenomic analyses of samples from more than 100 people with colon cancer. By integrating the data from several types of genomic and proteomic analyses from individual patients, they created patient tumor-specific proteogenomic atlases that revealed many new potential targets for personalized colon cancer treatment. One potential target they found is a protein called CDK2. Drugs that block the activity of CDK2 may potentially suppress the growth of colon cancer cells by restoring the normal function of a tumor suppressor gene.

Predicting Treatment Responses

One challenge in moving proteomics into the clinic alongside genomics is collecting enough tumor tissue. The amount of tumor typically collected during a biopsy is sufficient for DNA and RNA analysis, but more tissue is needed to analyze tumor proteins.

In 2020, NCI-funded researchers at the Broad Institute, Baylor College of Medicine, and their collaborators developed new methods of comprehensive proteomic analysis that require a smaller amount of tissue than has previously been possible. In a pilot study of patients with HER2-positive breast cancer, core needle biopsies of tumors obtained before and after treatment with the HER2-targeted therapy trastuzumab (Herceptin) were analyzed using the newly developed microscale approach. The analysis looked at both genomic and proteomic information to provide insights into why some patients’ tumors responded to treatment while others did not. The proteomic information suggested mechanisms of treatment response, lack of response, and drug resistance that would not have been evident with genomic information alone. This research also proved that these types of proteogenomic analyses can be performed with routine clinical samples.

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Today, nearly 40% of adults and 20% of children are obese, and those percentages are increasing. By 2030, researchers project that obesity will affect nearly half of US adults. Without intervention, the obesity epidemic will result in more cancers. Obesity is a disease that affects all aspects of the cancer continuum, including cancer risk, cancer detection and diagnosis, response to cancer treatment, and survivorship. Not only is obesity associated with a higher risk of 13 types of cancer, it is also associated with poorer survival rates for several types of cancer, including leukemia, breast, colon, and prostate.
Obesity increases the risk of death for all cancers combined.

- And yet 35% of cancer survivors are obese.
- And less than 17% meet physical activity guidelines.
- And only 10% eat the recommended amount of fruits & vegetables.

Percentage of U.S. population considered obese:

- Men: 52%
NCI is addressing this public health crisis in several ways. The institute funds research to understand the molecular and physiological mechanisms that explain the associations between obesity and cancer risk, treatment response, and recurrence. NCI-funded researchers are also focused on understanding how behaviors such as physical activity, diet, and sleep—and their associated psychological, social, and biological underpinnings—affect obesity.

Obesity increases the risk of other diseases, including cardiovascular disease and diabetes, while intentional weight loss has been shown to reverse some obesity-associated disease risks. For example, people who have had bariatric surgery have a reduced risk of breast, colon, endometrial, and pancreatic cancers compared with their obese peers who did not undergo bariatric surgery. Taking a multifaceted approach to address the highly complex challenges that obesity presents is essential. This includes NCI collaborating with other NIH institutes and centers to facilitate research opportunities to enhance our understanding of obesity.
In addition, the COVID-19 pandemic has created new challenges. For example, there is a need to understand the complex interplay between obesity and immune responses to infectious diseases, such as COVID-19. That interplay creates a potential risk of severe complications for patients with obesity and cancer. Another concern is the conditions created by the pandemic that may promote weight gain, such as stress and isolation.

More research is needed to fully understand how obesity affects cancer risk, progression, and treatment and to develop more precise strategies to prevent obesity and promote weight loss to reduce cancer risk and improve survivorship. As researchers identify the metabolic and behavioral factors that link obesity and cancer, it may be possible in the future to target interventions to reduce an individual’s cancer risk or improve outcomes for patients. For example, emerging evidence suggests that metformin, which is commonly used to treat diabetes, may also exert chemopreventive and antitumor effects in some cancers.

**Uncovering the Biology at the Intersection of Obesity and Cancer**

Obesity is linked to changes in metabolism, hormone signaling, inflammation, and microbiome function—all of which influence cancer risk, response to treatment, and recurrence through mechanisms that are still being investigated. Unraveling causal relationships is necessary to understand why obesity predisposes people to certain cancers, and to develop interventions based on these molecular mechanisms.

For example, obesity is associated with an increased risk for pancreatic cancer. Multiple mechanisms are attributed to obesity’s role in pancreatic tumor initiation, progression, and metastasis. One of those mechanisms is chronic low-grade inflammation. Chronic inflammation can cause DNA damage and inhibit DNA repair, leading to a higher rate of mutations. Chronic inflammation can also create an immune-suppressed environment conducive to cancer cell growth.

In addition, obesity can increase the risk of type 2 diabetes, which is also associated with an increased risk for pancreatic cancer. Researchers have identified many overlapping and distinct mechanisms of diabetes and obesity that also drive pancreatic cancer. NCI is currently supporting several initiatives to better understand the link between pancreatic cancer and diabetes.

**Addressing the Challenge of Childhood Obesity**

Childhood obesity rates have been steadily increasing over the last several decades. NCI collaborates with other federal and nonfederal partners to support research and interventions to address childhood obesity, which raises the risk of cancer and metabolic conditions and complicates the care of patients with cancer. One example is the [National Collaborative on Childhood Obesity Research](https://www.ncoob.org).

As many as one in three pediatric patients with newly diagnosed acute lymphoblastic leukemia (ALL) is overweight or obese, and pediatric obesity has been shown to have an adverse impact on ALL relapse and survival. Ongoing research is focused on identifying the underlying biological mechanisms to explain why. NCI-funded researchers are also investigating both medical and behavioral interventions to improve outcomes in overweight and obese children with cancer.

**Understanding the Link between Obesity and Early-Onset Cancers**
Research, including studies supported by NCI, suggests that obesity early in life may also increase the risk of developing certain cancers at an earlier age. For example, colorectal cancer incidence and mortality are increasing among people below the age of 50, and research suggests that obesity may be one of the contributing factors.

NCI-funded scientists at the Washington University School of Medicine, Harvard University, and their collaborators reported in 2019 that a high body mass index in early adulthood was associated with a risk of early-onset colorectal cancer among women participating in the Nurses’ Health Study II. More research needs to be done to understand how weight and other factors, including biological and environmental, contribute to early-onset cancers.

**Treating Patients with Obesity and Cancer**

Obesity affects cell metabolism throughout the body and may enhance or reduce the effectiveness of cancer treatment. As just one example, NCI-funded research has shown that fat cells can sequester and metabolize the chemotherapy drug daunorubicin (Cerubidine), thus reducing its effectiveness on tumor cells. In this way, the chemotherapy is less effective in patients with obesity, even when the dose is adjusted for body weight.

In contrast to chemotherapy, preliminary evidence suggests that obesity is associated with a better outcome among patients with cancer treated with immunotherapy, although the effect is still not well-understood. Obesity can also alter the composition and activity of the microbiome throughout the body, which affects the immune system. Much more research is needed to tease out the interactions between obesity and cancer treatments to inform patient care.

**Developing Behavioral Strategies for Weight Loss to Reduce Cancer Risk and Improve Patient Outcomes**

Research to develop and test individual and community-based behavioral interventions for weight loss will help improve health overall as well as prevent cancers and improve cancer outcomes in patients and survivors. The goal is to develop precise behavioral interventions—that include components involving diet and physical activity—so that individuals can not only achieve the difficult goal of losing weight, but also sustain that loss over time.

**Testing the Impact of Weight Loss on Survivors of Cancer**

Studies evaluating the impact of returning to a normal body weight from an obese state suggest that weight loss may decrease rates of cancer recurrence in patients with breast and prostate cancers, but additional clinical trials are needed to confirm these findings. To that end, NCI is funding a large phase 3 trial to test whether a weight loss intervention can reduce recurrence and prolong survival among breast cancer patients and survivors.

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**Helping Cancer Survivors Eat Better and Exercise More**

Wendy—University of Alabama at Birmingham
Another NCI-funded clinical trial is evaluating the impact of a weight loss intervention on overweight and obese men with localized prostate cancer under active surveillance. The goal of this trial is to evaluate whether weight loss improves health-related quality of life and prostate cancer progression.

Tailoring Weight Loss Interventions to Reduce Cancer Disparities

Cancer risk is greater for non-Hispanic Black adults compared with Hispanic or non-Hispanic White adults. Obesity may be one contributing factor, as the prevalence of obesity is highest among non-Hispanic Black adults (38.6%) compared with Hispanic adults (32.6%) and non-Hispanic Whites (28.6%). Disparities in obesity and cancer risk also exist between rural and urban populations. The prevalence of obesity is significantly higher among adults living in rural areas than among those living in metropolitan areas.

NCI supports research to understand the reasons for these disparities and to develop new strategies to address them. This includes research on environmental factors that contribute to obesity, including food and transportation systems and human-made parts of the environment where people live and work (for example, homes, buildings, sidewalks, and recreational spaces).

Addressing inequities in obesity among racial and ethnic minority populations has proven to be challenging. Factors that contribute to health disparities are embedded at the individual, interpersonal, community, and societal levels. The complex and dynamic interplay of these multiple levels of influence perpetuate health inequities. NCI funds research that elucidates the various causes of obesity and cancer disparities so that all populations benefit from scientific advancements to improve health. Just one example of NCI-funded research in this area is the adaptation of effective weight loss interventions, including dietary and physical activity strategies, in a culturally relevant manner for cancer survivors from diverse racial and ethnic groups.

Understanding Factors Contributing to Weight Loss Maintenance

With NCI’s support, researchers have developed effective strategies to initiate weight loss, but maintaining weight loss over time remains a challenge. Individuals differ greatly in their ability to maintain weight loss. NCI, in collaboration with the National Heart, Lung, and Blood Institute, is supporting efforts to understand the precise biological, psychological, social, and environmental influences that contribute to successful and sustained weight loss.

Adding to the complexity, evidence suggests that many genes, gene variants, and mechanisms that regulate gene expression contribute to varied responses to weight loss interventions. Genome-wide association studies (GWAS) have implicated genes from several biological pathways in obesity. These studies have revealed genes involved in pathways influencing appetite and satiety regulation, insulin secretion and function, formation of fat cells, and energy metabolism that contribute to obesity, variation in body mass index, and weight maintenance. More research is needed to understand the biology of these obesity-associated genes. NCI supports research to understand the complex interplay of genetics and behaviors and to identify genetic predictors of treatment response to behavioral weight loss interventions.

Improving the Measurement of Health Behaviors

NCI researchers are working collaboratively to develop better methods to precisely measure patterns of physical activity, diet, and sleep that, until now, have been studied in silos. The sophistication and wide-spread use of digital devices, such as smart watches, to monitor sleep and activity patterns continuously has made it easier for researchers to study 24-hour behavioral patterns. Smart phone apps have expanded the capacity to track dietary intake on a 24-hour basis more accurately and inexpensively. When combined, such technologies
expand data quality and accuracy, which is essential to understand how behavioral patterns may influence obesity and overall cancer risk.

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The number of cancer survivors has grown dramatically over the past several decades, a trend that is expected to continue as diagnosis and treatments improve. In 2019, the number of cancer survivors reached more than 16.9 million in the United States, and that number is expected to grow to more than 22.2 million by 2030.

The number of cancer survivors in the United States is projected to grow to 26.1 million by 2040. NCI considers a person to be a cancer survivor from the time of diagnosis until the end of life.


cancer.gov
An individual is considered a **cancer survivor** from the time of diagnosis, through the balance of his or her life. Survivors include those living with cancer and those free of cancer.

NCI-funded research has played a vital role in identifying the unique medical and psychological needs of both children and adults with a history of cancer. This includes NCI-funded studies documenting the large burden of late effects of cancer and its treatment. NCI is also funding research on the racial and ethnic disparities that exist throughout the cancer care continuum, including in survivorship.

**Challenges That Cancer Survivors Face**

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

Continued research will help us to understand and find ways to address the challenges that cancer survivors face. NCI-funded researchers are working to develop effective interventions that mitigate the short- and long-term adverse effects of cancer and its treatment, based on the mechanisms that cause them. NCI is also actively supporting research to understand how to improve the delivery of care to cancer survivors. In addition, improving the quality of life of survivors requires research to better understand the role of diet, exercise, and other modifiable risk factors. NCI’s work in these areas will support new ways to greatly improve the well-being and quality of life of cancer survivors.

**Improving Survivorship after Cancer in Early Life**

The potential burden of the long-term effects of cancer and its treatment are particularly salient for survivors of **pediatric cancers**. Due to major advances in treatment, 80% of children (aged 14 and younger) and adolescents (aged 15–19) treated for cancer will now survive 5 years or more. Yet, many treatments that are effective in curing cancer can also cause adverse effects that appear years later. Continued research will help us to better understand these late effects and develop strategies to mitigate them.
effective against cancer increase the risk of conditions that can impair the quality and length of life, such as heart problems, infertility, cognitive deficits, and second cancers. There is also emerging evidence that survivors of pediatric cancer experience the effects of accelerated aging (for example, frailty, comorbidities, or a decline in exercise capacity) and reduced life expectancy.

Longstanding studies such as the NCI-funded Childhood Cancer Survivor Study and St. Jude LIFE Study have enabled researchers to identify these late effects of cancer and its treatment. For instance, in 2017, NCI-funded researchers at St. Jude Children’s Research Hospital published a comprehensive account of the large and diverse set of aging-related chronic health conditions faced by childhood cancer survivors compared with individuals of the same age without a history of cancer.

More research is needed to understand the biological mechanisms underlying these effects and to develop new ways to prevent and mitigate them. As part of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018, NCI is working to improve the care and quality of life of childhood, adolescent, and young adult cancer survivors by supporting research across multiple domains, including the impact of familial, socioeconomic, and environmental factors on survivor's outcomes.

Specifically, NCI is supporting a series of studies testing new interventions to prevent and manage late and long-term treatment effects, such as burdensome symptoms, sedentary behavior, and neurocognitive dysfunction. Other research is testing approaches to survivorship care delivery that will improve outcomes and reduce the burden of cancer morbidity. These studies are also exploring the use of technology to combat sedentary behavior and to identify and manage problematic symptoms in real-time.

Part of NCI’s efforts to expand childhood cancer biobanking also align with the STAR Act. These efforts to increase specimen collection and genomic sequencing of survivors diagnosed with subsequent cancers and those experiencing chronic health conditions will aid the biological understanding of long-term effects of treatment for childhood cancers.

NCI is also investing in the Childhood Cancer Data Initiative (CCDI), which includes the development of a National Childhood Cancer Registry. The registry will build upon and complement existing cancer registry efforts led by both NCI and the Centers for Disease Control and Prevention. Resources developed through the CCDI will help support scientists by improving the availability and usability of data from this important patient population. These efforts will also leverage new methods in data science to study the long-term health of childhood, adolescent, and young adult cancer survivors.

Understanding, Preventing, and Mitigating Long-Term Effects of Cancer Treatment

Long-term side effects of some cancer treatments can also impair the length and quality of life of cancer survivors diagnosed as adults. NCI funds a wide range of research to identify these effects and to test interventions to prevent and mitigate them. For example, NCI-supported cancer survivor cohort studies help researchers to identify and understand the long-term effects of cancer treatment as well as other factors that impact the health of survivors.

Heart damage, for example, is a side effect of some cancer drugs, such as the chemotherapy agent doxorubicin that is used to treat several types of cancer. Researchers are actively testing strategies to reduce
the toxicity of drugs and protect cardiac function during cancer treatment. For example, with NCI funding, researchers at Albert Einstein College of Medicine and their collaborators recently found that an experimental drug called BAI1 prevented heart damage from doxorubicin in mouse models of breast cancer and leukemia. BAI1 prevented the death of heart cells and did not interfere with doxorubicin’s ability to kill cancer cells. The researchers plan to conduct a clinical trial to continue testing this strategy.

Some patients with metastatic cancers treated with immunotherapy, such as immune checkpoint blocking drugs for melanoma or non-small cell lung cancer, are surviving many years after their diagnosis. Yet, while these drugs can have serious and acute side effects, little is known about their long-term effects. To fill this knowledge gap, NCI is funding research to follow patients treated with immunotherapies and study the long-term impacts of these treatments.

Long-lasting cognitive changes that occur in children, adolescents, and adults who are treated with chemotherapy are well documented, but little is known about the mechanisms that contribute to these cognitive problems. Interventions to prevent or ameliorate them are only in their infancy, and NCI is actively soliciting research proposals that leverage recent discoveries in cognitive neuroscience to study this phenomenon. The long-term effects of newer therapies are not well known, and more research is needed to investigate them as well.

These examples highlight just a few of the areas of research NCI is pursuing to better understand, prevent, and mitigate the harmful effects of cancer treatment to improve long-term outcomes for cancer survivors.

Understanding How to Improve the Delivery of Survivorship Care

NCI supports research to improve the delivery of care for cancer survivors in diverse settings. Challenges for the care of survivors can include, for example, the transitions from pediatric to adult care settings or from specialty to primary care settings.

After cancer treatment ends, a patient’s transition from receiving care from an oncology team to a primary care team is challenging for many reasons. One reason is that the current model relies heavily on the patient’s ability to communicate and facilitate the transition, but many patients cannot maintain that role. There is also a need to better understand what tools and resources primary care providers need to ensure they are well-equipped to provide survivorship care. With support from the Cancer Moonshot™, NCI is supporting research on interventions that enhance communication, collaboration, and coordination among oncologists and other health care providers to improve outcomes for cancer survivors.

NCI-supported researchers are also seeking to better understand how to tailor the level of survivorship care based on an individual’s specific needs. For instance, certain patient subgroups may warrant more intensive follow-up care than others based on, for example, risk of recurrence or the physical or physiological effects of their cancer and its treatment. NCI is currently seeking new ideas from the research community to address this need.
Improving Outcomes through Healthier Lifestyles

Research studies have suggested that engaging in physical activity, eating a healthy diet, maintaining a healthy weight, and other health behaviors may improve the quality and length of life for survivors of certain cancers.

In 2019, the American College of Sports Medicine updated its recommendations on the role of physical activity in cancer survivorship and prevention. Research funded by NCI and others provided evidence to conclude that aerobic and/or resistance training can improve physical functioning, health-related quality of life, and common cancer-related health outcomes, including anxiety, depressive symptoms, and fatigue. In 2020, an NCI-funded study added to the evidence linking exercise with longer survival in women diagnosed with high-risk breast cancer.

NCI is also supporting research on weight and weight-loss strategies in survivors of cancer, including different racial and ethnic populations. NCI has funded a range of additional research on behavioral factors and cancer survivorship. Yet, many questions still need to be answered to provide more precise guidance to cancer survivors during and after treatment.

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