Annual Plan & Budget Proposal for Fiscal Year 2024

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DIRECTOR'S MESSAGE

For much of the past 50 years, a melanoma diagnosis was essentially a death sentence. Today, thanks to advances in cancer research, the outlook for people with melanoma—and several other cancers—has dramatically improved.

Over the course of my career, I have seen countless examples where cancer research has given hope to people who might once have had none. With the scientific opportunities available to us today and the right investments, we can create many more reasons for hope.

The extraordinary progress we have seen was made possible by decades of investments in basic, translational, clinical, and implementation research. Thanks to these advances, I am confident that we can end cancer as we know it—not only for a lucky few, but for all.

For instance, efforts to develop drugs that target mutant forms of KRAS, which drive more than 30% of cancers and were long considered undruggable, hit a major milestone in 2021: the first approval of a KRAS inhibitor. And more such drugs are on the horizon. Meanwhile, although lung cancer is still one of the leading causes of cancer death, its toll has dropped more rapidly in recent years, thanks to the combination of tobacco prevention and cessation, screening, and an explosion of Food and Drug Administration approvals for new drugs—including targeted therapies and immunotherapies—since 2010.

As a young cancer researcher decades ago, I could not have imagined the incredible scientific resources available to today's researchers thanks to NCI support across the cancer research enterprise. For instance, many scientists supported by NCI grants conduct their research at state-of-the-art facilities, such as the 71 NCI-Designated Cancer Centers, with access to sophisticated technology that would have seemed like science fiction not long ago. Researchers are taking advantage of resources such as NCI's National Cryo-Electron Microscopy Facility, Patient-Derived Models Repository, and Cancer Research Data Commons. Others are embarking on their careers through a wide array of NCI training programs and support for early-stage investigators.

Despite research advances that have led to steady—and, in some cases accelerating—declines in cancer death rates since the early 1990s, far too many people still face cancer's devastating effects. We can do so much more. We can prevent more cancers. We can diagnose cancers earlier. We can develop more effective—and less toxic—therapies. We can unravel the mysteries of even the rarest and most treatment-resistant cancers. And we can ensure that these advances are available to all.

NCI will pursue many scientific opportunities that have the potential to greatly accelerate progress. In this Annual Plan and Budget Proposal, we highlight four examples:

- **Multi-cancer detection tests**: The ability to screen blood or other body fluids for multiple types of cancer simultaneously in symptom-free people would represent an extraordinary advance, particularly for cancers like pancreatic, ovarian, and brain, for which no screening tests exist.
- **Cell therapy to treat cancer**: Therapies that use a patient's own immune cells to kill cancer cells have been approved for patients with certain blood cancers. Cell therapy could offer a treatment option for solid tumors, which comprise about 90% of all cancer diagnoses.
- **Persistent poverty and cancer**: We need to better understand how persistent poverty impacts different populations, as this is a multigenerational, population-level problem that exacerbates cancer.
- **"Undruggable" cancer targets**: Drugs that target cancer-driving proteins that have eluded all attempts to stop them could result in new strategies to target almost any abnormal protein and lead to medicines for more patients.

The Cancer Moonshot℠, initially launched in 2016, has helped NCI unleash many more opportunities for cancer research. The Cancer Moonshot has established important networks of scientists who collaborate on a greater scale. The Pediatric Immunotherapy Discovery and Development Network, for example, has made advances such as improving the cancer-fighting ability of CAR T cells.

The Cancer Moonshot has also enabled NCI to build infrastructure with the unprecedented capabilities to share cancer data across the research community. For instance, the Human Tumor Atlas Network's three-dimensional cancer atlases will help researchers understand and intercept tumor growth at any stage. Additional investments outlined in the Professional Judgment Budget Proposal will ensure that we build on the Cancer Moonshot's successes thus far and further catalyze progress to achieve the bold goals put forth by President Biden.

This Annual Plan and Budget Proposal describes the resources needed to ensure that the cancer research enterprise remains strong, delivers on the opportunities before us, and transforms what it means to have cancer. Because fundamental scientific discovery is the backbone of cancer research, we must make strong investments in investigator-initiated research aimed at unlocking cancer biology and increasing the pipeline of new, less toxic drugs for cancer prevention, interception, and treatment.

NCI will also continue to expand and modernize clinical trials to reach more people, so that everyone benefits, no matter their demographics. Through implementation science, NCI aims to better understand how to ensure current and new standards of cancer care reach all patients equitably. All of these efforts depend on a cancer research workforce that reflects the populations we serve. To that end, NCI will expand its efforts to recruit more early-stage investigators from diverse backgrounds, further leverage existing programs that train members of underrepresented groups, and drive cultural change at the institution level that embraces equity, inclusion, and diversity of thought.

As I consider what we can achieve through cancer research, I am humbled by the advances made possible by the many people with cancer who have participated in research, and I am filled with hope. What once seemed so far off is closer than ever. By harnessing the incredible talent and dedication of the cancer research workforce, building on decades of scientific discovery, and taking advantage of today's cutting-edge technology, we can truly transform what it means to have cancer so that far more people live longer, healthier lives.

Douglas R. Lowy, M.D.

Acting Director
National Cancer Institute

NCI PROFESSIONAL JUDGMENT BUDGET PROPOSAL

NCI's proposal for a significant budget increase in fiscal year (FY) 2024 is designed to capitalize on important scientific opportunities in pursuit of the goal to end cancer as we know it for all people. These opportunities include

- the **exceptional ideas** being put forth by the cancer research community, reflected in the explosion of R01 applications in recent years. Investigator-initiated research supported through research project grants, including R01 grants, is the source of some of the most innovative and transformative ideas in cancer research.
- the need to **expand and modernize cancer clinical trials**, which are essential for moving new methods of preventing, diagnosing, and treating cancer from the laboratory to physicians' offices and other clinical settings to improve care and quality of life for people with cancer or those at risk of cancer.
- the successes of the Cancer Moonshot℠, which NCI will build upon to sustain the progress made through the 21st Century Cures Act and continue to improve our understanding of cancer and identify new approaches to prevent, detect, and treat cancer.
- a continued commitment to **advancing health equity and ensuring rapid dissemination and delivery of standards of care** so that the benefits of cancer research reach populations that, for too long, have not benefited fully from research progress.

With the necessary increases to NCI's budget and sustained investments over time, we can leverage the scientific and societal opportunities before us to deliver the research advances that the American people want and deserve.

Funding at the level proposed will also represent progress toward NCI's goal of increasing the R01 payline—that is, the percentile of R01 grant applications NCI can fund. NCI must also continue to support the expansive infrastructure and resources that are all vital parts of the National Cancer Program—from cutting-edge technology and unprecedented access to cancer data, to nationwide networks of scientists and research centers.

Additional key NCI investments include the

- NCI-Designated Cancer Centers, which deliver the latest cancer treatments to patients in communities across the United States, play an important leadership role in laboratory and clinical research, and provide training for biomedical researchers and health care professionals
- NCI clinical trials networks, which currently enable NCI to enroll patients at over 2,599 academic and community sites across the country
- Childhood Cancer Data Initiative, an ambitious effort in data collection, sharing, analysis, and access to improve the future for children, adolescents, and young adults with cancer
- Specialized Programs of Research Excellence (SPOREs), cornerstones of NCI's efforts to promote collaborative, interdisciplinary translational cancer research through grants that involve basic and clinical scientists working together to develop new approaches to the prevention, early detection, diagnosis, and treatment of cancer
- NCI Equity and Inclusion Program, which is addressing cancer disparities and growing a more diverse and inclusive cancer research workforce across all NCI programs

PROFESSIONAL JUDGMENT BUDGET PROPOSAL FOR FISCAL YEAR (FY) 2024

(DOLLARS IN MILLIONS)

Prior (FY 2023) Professional Judgment Budget Proposal	**$7,550***	
Proposed Budget Increase for FY 2024 to Seize Opportunities for Progress	**$1,166**	**$354** Cancer Biology Research **$247** Cancer Prevention Research **$192** Cancer Detection & Diagnosis Research **$227** Cancer Treatment Research **$86** Public Health & Cancer Control Research **$60** Training & Infrastructure
Funding to Revolutionize Cancer Clinical Research†	**$1,272**	
FY 2024 TOTAL	**$9,988**	

*This proposal includes $50 million for the Childhood Cancer Data Initiative, a 10-year initiative that began in FY 2020.
†This proposed funding will be used to achieve the goals of reducing cancer death rates by 50% over the next 25 years and ending cancer as we know it for all.

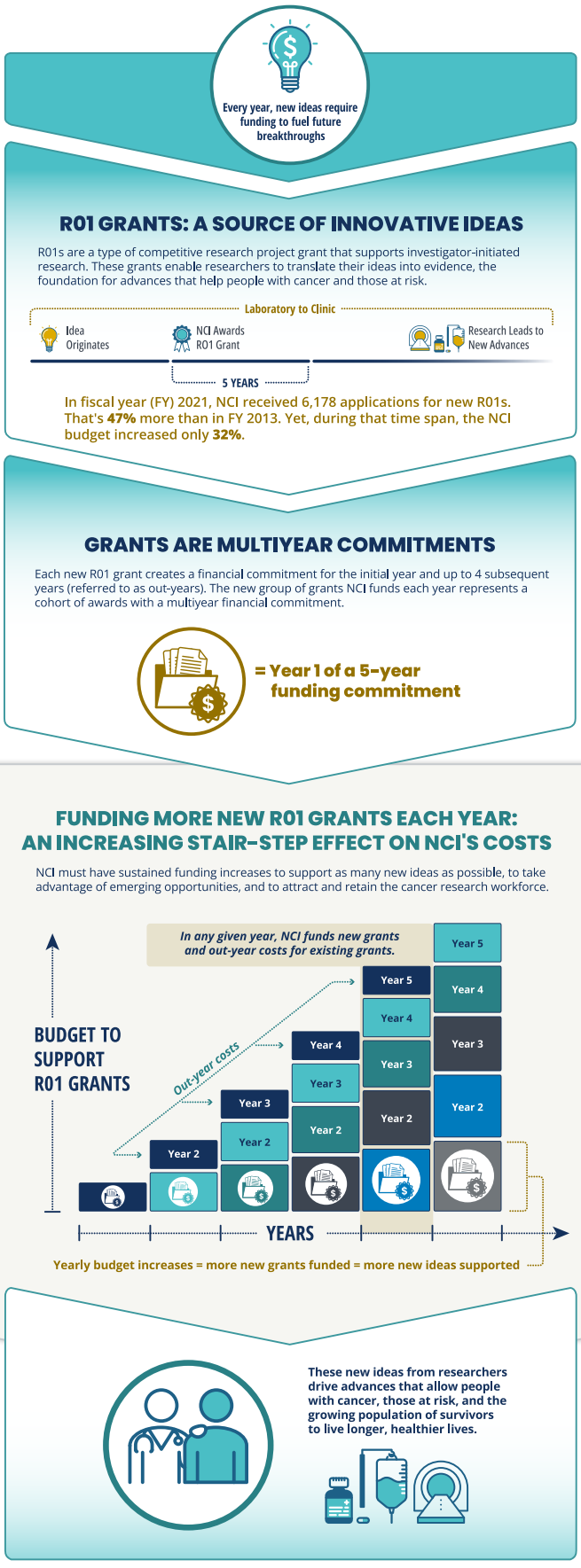
Sustained, robust increases are needed so we do not miss out on promising ideas

Investigator-initiated research is the main engine of innovation in the nation's biomedical research enterprise. Many major cancer research advances (such as targeted therapies and immunotherapies for patients with cancer, and vaccines and drugs to prevent cancer) grew out of such lines of inquiry. NCI must support as many new ideas as possible to ensure that we do not miss the most promising opportunities to make progress against cancer.

In FY 2021, NCI awarded more grants across all mechanisms than ever before—a testament to the enthusiasm and expertise of the cancer research community and sustained national investment in cancer research. Without robust funding increases, NCI's ability to make similarly aggressive investments in the future is limited.

Most NCI grants provide 5 years of funding to researchers. While this timeframe is necessary for testing ideas with sufficient rigor, the number of new grants awarded each year cannot grow without robust annual funding increases. NCI must support both the cost of grants that carry over from previous years (out-year costs) and the initial-year costs of newly awarded grants. When grants conclude, the allocation that would have gone to them becomes available to support new grants and out-year costs of grants made in previous years. However, this amount is not enough for NCI to increase the number of new awards, year after year. That can only be achieved through sustained funding increases that allow NCI to raise the R01 payline and fund more new ideas each year, particularly in the form of R01 grants.

WHY SUPPORTING THE BEST IDEAS IN CANCER RESEARCH REQUIRES FUNDING INCREASES OVER TIME



https://cancer.gov/about-nci/budget

Over much of the past decade, NCI has experienced a tremendous increase in R01 grant applications, outpacing budget increases. This means we support far fewer grants than we would like, and we are surely missing out on many ideas that could bring us that much closer to ending cancer as we know it. Greater difficulty securing funding for meritorious research also discourages current and future cancer researchers, which poses a further drag on progress.

NCI SUPPORT FOR THE CANCER RESEARCH ENTERPRISE

Allocating funds to raise the R01 payline must be balanced with maintaining other critical NCI programs.

Focusing on R01 grants, the payline for established investigators in FY 2019 was at the 8th percentile, down from the high of the 16th percentile in FY 2009. Thanks to Congress's continued support, NCI was able to increase the R01 payline to the 11th percentile in FY 2021, an increase of 37%. NCI has set a goal to reach a payline at the 15th percentile by FY 2025, as we believe this is the minimum payline needed to maintain the strength of the field.

Since FY 2018, the payline for early-stage investigators has been 5 percentile points higher than the payline for established investigators. NCI is committed to nurturing a pipeline of talented and diverse scientists to ensure the future strength of the cancer research workforce. Funding described in this proposal will enable paylines for early-stage investigators to grow from the current 16th percentile to the 19th percentile, enabling NCI to attract more scientists early in their careers through dedicated support.

Cancer Moonshot: New goals, new opportunities

Early in 2022, President Biden announced the reignition of the Cancer Moonshot with the goals of reducing overall cancer death rates by 50% in the next 25 years and improving the quality of life for all people living with cancer and cancer survivors. To achieve the President's goals and to change the experience of cancer as we know it, the whole-of-government approach must rest on a solid foundation of scientific research.

NCI is uniquely positioned to lead the research that will result in changes in standards of care for people with cancer and to conduct the implementation research needed to identify optimal methods to deliver research findings and other evidence-based knowledge into clinical practice. NCI will build on its legacy of directing the National Cancer Program and the progress made from research funded through the 21st Century Cures Act, which initiated the Cancer Moonshot.

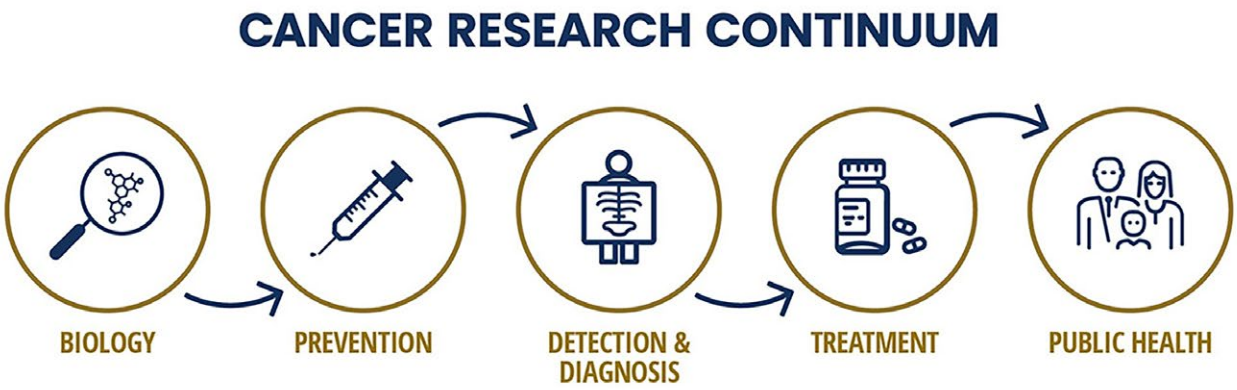
The initial Cancer Moonshot supported a wide range of cancer research goals that included accelerating discovery, increasing collaboration, and expanding data sharing. Over the past 6 fiscal years, NCI has funded almost 300 new projects that are delivering important insights into the mechanisms that drive cancer, addressing cancer disparities, identifying evidence-based strategies for health care delivery, and developing new approaches to prevent and treat cancer.

For example, patient-derived tumor models from diverse populations are being created, characterized, and shared with the research community to understand why certain populations sometimes respond differently to cancer therapies. Another Cancer Moonshot project is developing interventions to overcome barriers to colorectal cancer screening in American Indian populations. Also, Cancer Moonshot–supported networks are working to expand the benefits of immunotherapy for adults and children with cancer. The research done by the Immuno-Oncology Translational Network has led to new insights into how ovarian cancer responds to immunotherapy.

In this next phase of the Cancer Moonshot, NCI will sustain this progress and build upon these successes to continue to improve treatment outcomes and quality of life for all. With support from the White House and bipartisan congressional support, NCI can change the experience of cancer as we know it for all people, by focusing on the following:

- expanding and modernizing cancer clinical trials and the enterprise supporting them
- continuing to invest in basic and translational research to ensure a continuous stream of new approaches to cancer prevention, diagnosis, and treatment
- ensuring equitable health care delivery of current and new standards of care for cancer prevention, screening, and treatment
- expanding and enhancing the diversity of the cancer research workforce

NCI RESEARCH PORTFOLIO: DRIVING CANCER DISCOVERIES



NCI enables advances in cancer by investing in a broad portfolio of research, supporting the cancer research workforce, and sustaining the infrastructure that enables cutting-edge research to succeed.

Supporting high-impact cancer research

NCI funds the most promising research in established areas of science and seizes opportunities in emerging areas of science. NCI-supported research is underway in all 50 states, Washington, DC, and beyond.

Investing across the cancer continuum

NCI's overarching strategy focuses on supporting a broad portfolio of research, tackling the problem of cancer from many angles. Basic, translational, population science, and clinical research are essential to improve cancer prevention, detection, diagnosis, treatment, and survivorship.

- Cancer biology research supported by NCI drives virtually all major advances made against cancer.
- Cancer prevention research by NCI-funded investigators has contributed to the decline in the overall rate of cancer incidence in the United States during the last 25 years.
- Cancer detection and diagnosis research funded by NCI supports improvements in the identification and characterization of cancer and its precursors.
- Cancer treatment research funded by NCI, including basic and preclinical studies and the testing of new agents in clinical trials, has aided the development of most of the cancer therapies available today.
- Public health and cancer control research by NCI-funded investigators has improved the delivery of cancer care and enabled new interventions to improve cancer prevention, screening, treatment, and survivorship.
- Explore other areas of NCI's broad research portfolio.

Highlighted Scientific Opportunities

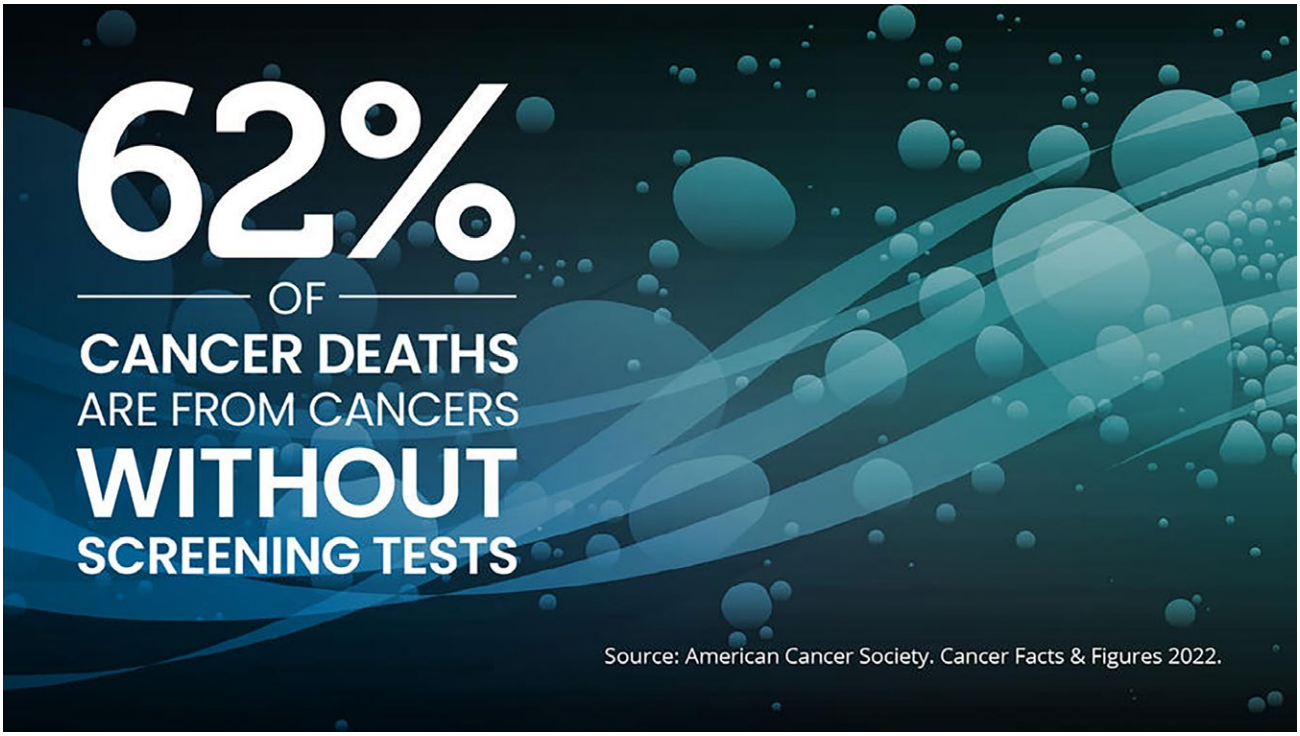
NCI continually pursues new and emerging scientific opportunities that, with further investment, would catalyze additional progress in cancer research. Read about four areas of opportunity highlighted in the Fiscal Year 2024 Annual Plan and Budget Proposal: multi-cancer detection, cell therapy to treat cancer, persistent poverty and cancer, and undruggable cancer targets.

Strengthening the cancer research enterprise

NCI has built and supported an infrastructure—consisting of people working in science and the places at which they work—that has become known as the cancer research enterprise. NCI's investments in the cancer research workforce and in world-class facilities and resources include the following:

- Training the next generation of cancer researchers and building and sustaining a talented and diverse workforce will poise the cancer research community to make the breakthroughs of the future.
- NCI-Designated Cancer Centers develop and translate scientific knowledge from promising laboratory discoveries into new treatments for patients with cancer.
- NCI's National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) conduct cancer prevention, treatment, and cancer care delivery research in diverse settings throughout the United States, Canada, and internationally.
- NCI partners with federal and private-sector organizations to facilitate complex research programs that spur innovation, ensure the judicious use of public resources, and continue to help reduce the burden of cancer in the United States and beyond.

ASYMPTOMATIC MULTI-CANCER DETECTION: ADVANCING CANCER SCREENING TO SAVE LIVES



The overall goal of cancer screening is to reduce suffering from cancer and save lives by identifying precancer or cancer before it causes symptoms. For example, colorectal cancer screening substantially reduces the risk of developing and dying from colorectal cancer and screening mammography can reduce deaths from breast cancer. Although these screening tests and other methods successfully detect precancers and early cancers in people without symptoms, the tests are limited to only a few common cancer types. For many cancers, there are no effective screening tools. Symptoms of deadly late-stage disease for these unscreened cancers may be the first sign that something is wrong.

Asymptomatic multi-cancer detection (MCD) tests have the potential to substantially change this narrative. Using a single blood draw, these tests may be able to detect the presence of multiple cancer types—including ones without established screening methods.

What Is Multi-Cancer Detection?

Multi-cancer detection (MCD) tests pick up signals in blood and other body fluids that may suggest the presence of cancer. They are the latest versions of a technique known as liquid biopsy. Such approaches seek out cancer clues, such as circulating tumor cells, tumor DNA, and other tumor materials that cancer cells release into the body. MCD tests can process these signals and predict the presence of different types of cancers.

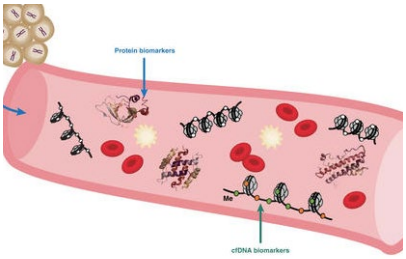
This promising new technology has the potential to transform how we think about and implement cancer screening. However, many questions about the benefits and harms of using MCD tests for cancer screening remain unanswered. It is unknown whether MCD tests will reduce deaths from cancer, lead to unnecessary diagnostic procedures that may cause undue harms, or change the use of standard, effective screening tests. Additionally, we don't know if all populations will benefit equally from this technology.

To answer such questions, we need to conduct rigorous clinical trials to determine whether using MCD tests to screen asymptomatic people will reduce cancer deaths without causing substantial harms, such as suffering and long-term anxiety from inconclusive or negative diagnostic investigations triggered by a positive result on a MCD test.

NCI is supporting the creation of a new clinical trials network tailor-made to evaluate these and other emerging screening technologies. Investments in assay research and development will also fuel discoveries that may enhance existing MCD tests and catalyze the generation of new methods.

Although it may seem counterintuitive, detecting asymptomatic cancer does not necessarily save lives. For example, chest x-rays can detect some lung cancers before they become symptomatic, but rigorous clinical trials did not show that identifying lung cancers with chest x-rays prevented death. By contrast, screening with low-dose computed tomography can reduce deaths from lung cancer.

Current MCD tests are better at detecting later-stage cancers than early-stage disease. Therefore, it is critical to determine whether these tests will reduce mortality compared with not using such tests.



SCREENING FOR MANY CANCERS WITH ONE TEST

Many multi-cancer early detection tests are in the works, but more research is needed.

Designing a new screening network

NCI has a long history of conducting pivotal clinical trials. The National Clinical Trials Network (NCTN) has conducted seminal cancer treatment trials for decades. The NCI Community Oncology Research Program (NCORP) has conducted important cancer prevention and control clinical trials and brings cancer clinical trials and care delivery studies to people in their own communities.

A new Cancer Screening Research Network (CSRN) will build upon the clinical trials infrastructure that is already in place with these established networks. CSRN will focus on fostering relationships with primary care physicians, gynecologists, gastroenterologists, and other clinicians, as well as health outcomes researchers and population scientists. Such health care providers have expertise in screening people without symptomatic cancer. This screening network will establish study sites across the United States and enable diverse and representative populations to participate in cancer screening studies.

One of the first areas of investigation for this network will be to study whether these promising MCD tests, when used for cancer screening, will prevent cancer deaths and for whom. Answering this question is an urgent matter: Some of these tests are already available to the public, although none have been proven to reduce mortality.

NCI is already contributing to efforts to determine the broader impact of MCD tests on public health. Researchers at the Fred Hutchinson Cancer Research Center, the University of Washington, and NCI developed a framework for calculating the benefit-versus-harm profile of an MCD test. Their analysis points to the number and type of cancers to include in multi-cancer screening, criteria that can lead to more lives saved while limiting harms.

Key Unanswered Questions about Multi-Cancer Detection

Research is needed to assess the impact of multi-cancer detection tests, including

- Do the tests reduce a person's likelihood of dying from cancer?
- Do the tests work equally well in all populations?
- What procedures should be followed if a test indicates cancer?
- What follow-up is required if no cancer is found after a positive test result?
- What harms, such as complications from unnecessary invasive procedures, do these tests cause?
- Will people undergo recommended screening methods, such as mammograms and colonoscopies, after using these tests?
- Will these tests help address health disparities or make them worse?

This effort to study the impact of MCDs extends across NCI—and beyond. There are ongoing discussions with federal partners, such as the Food and Drug Administration, the Centers for Medicare and Medicaid Services, the Department of Veterans Affairs, and the Department of Defense. NCI is also actively engaging with a variety of interested parties outside the government. The institute issued a request for information specifically seeking information from companies to learn more about technologies in development and to gauge interest in a clinical trial. Conversations with respondents are ongoing. NCI is also planning to conduct focus groups to understand public perception of the benefits and risks of using MCD tests for cancer screening.

Leveraging investments in technology and tumor biology to detect asymptomatic cancer

NCI has played a foundational role in developing MCD tests through investments in cancer biology as well as technology development. These investments enabled a first-of-its-kind study, led by Johns Hopkins University researchers, that successfully combined imaging with a multi-cancer blood test called CancerSEEK to detect tumors in participants with no symptoms or history of cancer. The test is now under further development with a cancer biotechnology company.

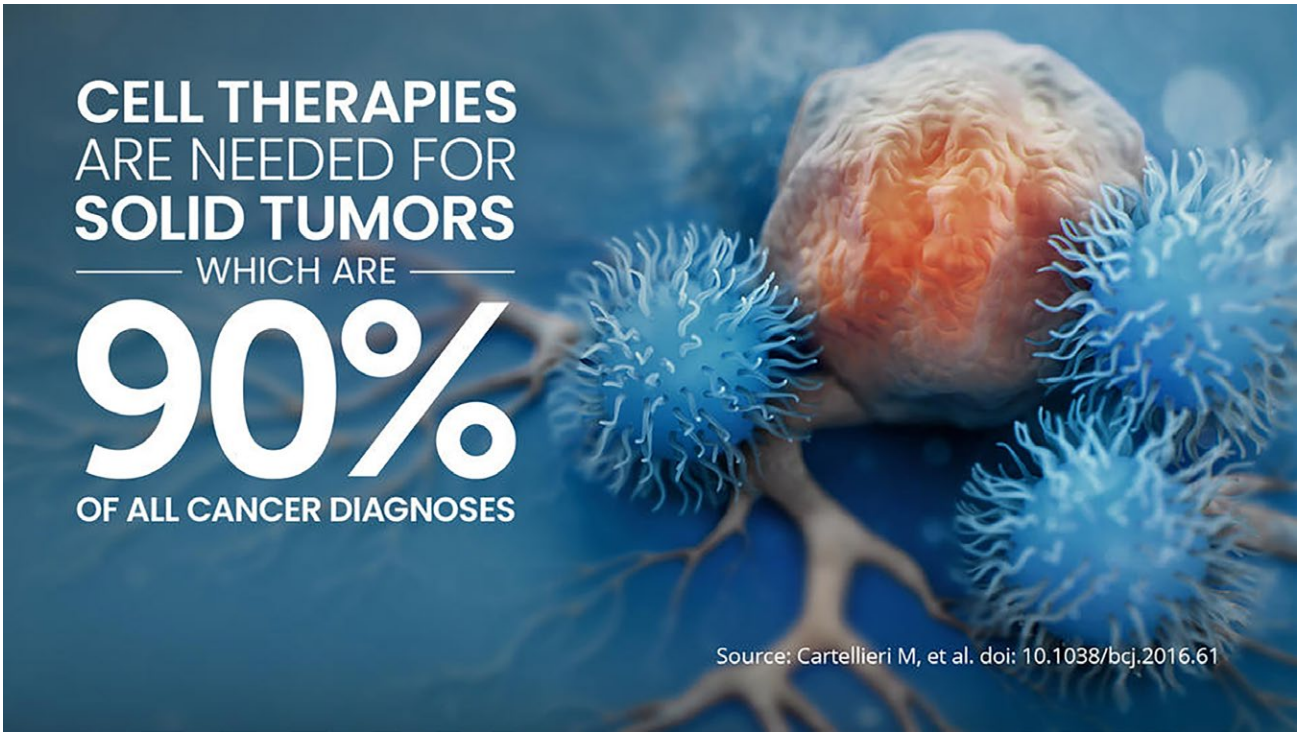
NCI continues to play a driving role in advancing liquid biopsy technology through the NCI-supported Liquid Biopsy Consortium. Multidisciplinary teams across the country are working on blood-based liquid biopsy tools for the detection of asymptomatic breast, ovarian, and lung cancer, as well as exploring detection of asymptomatic cancers using cerebral spinal fluid, saliva, and stool.

In addition to these investments in technology research, NCI-supported studies of basic cancer biology serve as a starting point to identify measurable features for early cancer detection. For example, NCI-funded researchers found that a fragmented pattern of cell-free DNA in the blood is common in patients with cancer. By combining cell-free DNA fragmentation and mutation analysis with artificial intelligence machine learning, the researchers accurately detected 91% of cancer cases in their study, which included breast, colorectal, lung, ovarian, pancreatic, gastric, and bile duct cancers. It remains to be determined whether this approach will prove useful in identifying and benefiting patients not known to have cancer.

These are just a few examples from a large portfolio of NCI-supported research in cancer biology that spans decades. NCI will continue to spearhead exploration into the differences between healthy cells and cancer cells to translate that knowledge into novel screening technologies and ways to intercept cancers before they become lethal. Discoveries will accelerate the development and refinement of MCD tests. The new CSRN will also provide an infrastructure for evaluating these emerging approaches in diverse populations.

As NCI makes these foundational investments in MCD and other screening technologies, we'll learn more about how to screen for cancers to save lives. By rigorously evaluating MCD tests and ensuring that the benefits outweigh potential risks, we may be able to take important steps toward ending cancer as we know it today.

CELL THERAPY: HARNESSING CELLS OF THE IMMUNE SYSTEM TO FIGHT CANCER



One of the most exciting developments in the fight against cancer is the advent of cell-based immunotherapy, a personalized treatment that kills cancer by using the patient's own immune cells. To date, cellular therapies have been approved for people with certain blood cancers, but cell therapy for solid tumors has yet to reach that same milestone. With solid tumors comprising about 90% of all cancer diagnoses, more research on cell therapy technology and scalable production could expand this treatment to a much larger number of people with cancer.

Cell therapy uses living cells as a drug to treat disease. When used to treat cancer, cell therapy takes advantage of the immune system's intrinsic ability to seek out and destroy abnormal cells in the body. This approach goes by many names, including immune cell therapy and adoptive cell therapy, but they all refer to the same type of cancer treatment. Specialized immune system cells are either 1) engineered to recognize unique tags on an individual's cancer or 2) selectively isolated from a patient's tumor and grown in large numbers in the laboratory and given back to the patient by intravenous infusion.

Over the past decade, NCI-funded studies have established cell therapy as a viable cancer treatment strategy, and NCI-supported researchers continue to refine and expand on that work. Today, there are 36 NCI-Designated Comprehensive Cancer Centers with cell therapy programs and the Food and Drug Administration (FDA) has approved six cell therapies to treat blood cancers. However, developing cell therapies for solid tumors that will selectively attack cancer cells, persist in the body, and overcome a tumor's ability to hide from the immune system has been notoriously difficult. Cell therapy is also very expensive and difficult to produce in scalable quantities with the technologies available.

Fundamental laboratory research is needed to break through these barriers to expanding cell therapy. With research findings in hand, additional federal funding will enable early-phase clinical trials that test novel cell therapy approaches. The federal government also plays an important role in providing the infrastructure and shared resources that facilitate cell therapy studies at research centers and clinical trial sites around the country.

If we can adapt cell therapy to successfully treat solid tumors plus sustain NCI-supported infrastructure development, many more patients could benefit from this individualized, highly targeted cancer treatment.

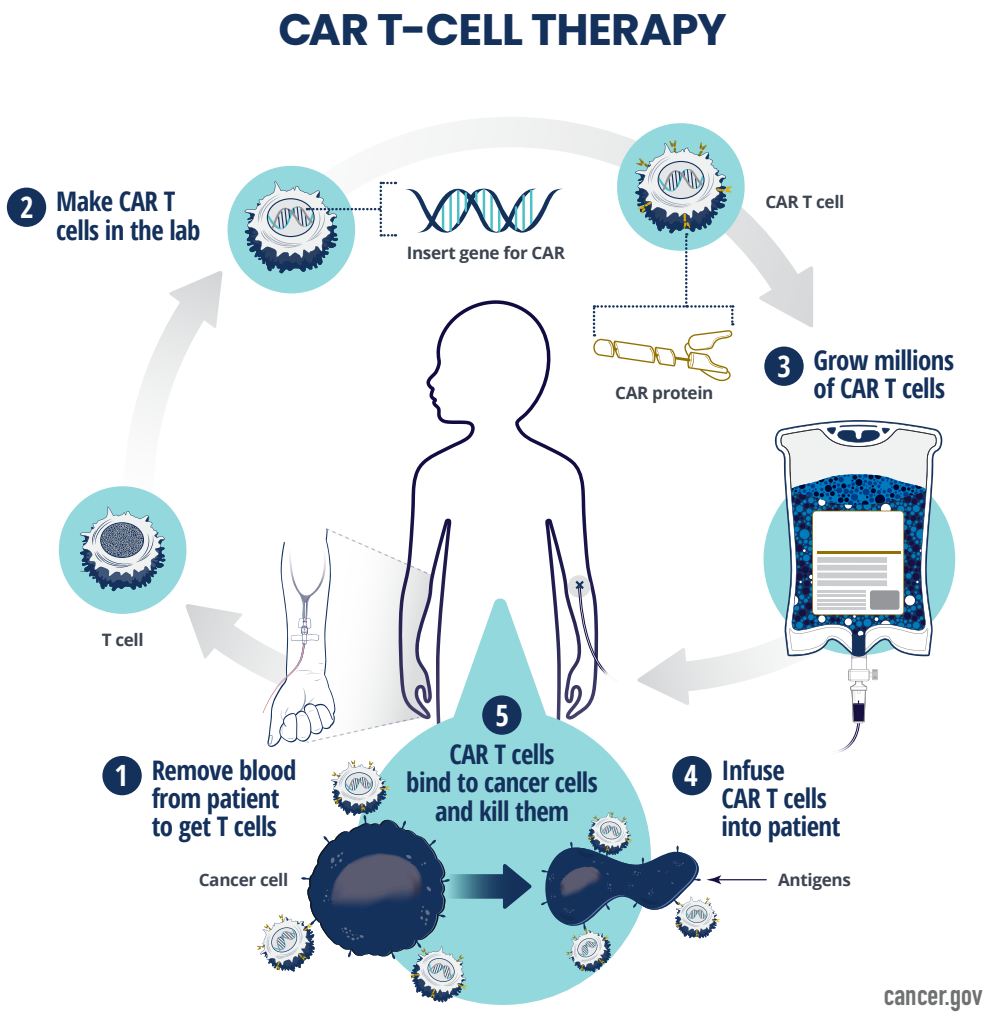
Targeting solid tumor cells without harming healthy tissue

A key requirement for cell therapy is the identification of molecules that are found predominantly, or only, on cancer cells. The lack of cancer-specific molecules that mark solid tumors has been a major barrier to bringing cell therapy to more people with cancer. This is particularly challenging for childhood cancers because tumor cells and healthy cells in children share many of the same molecular tags.

Over the past few years, NCI investments have bolstered tumor marker discovery for solid tumors, including those that arise in children. In 2019, an NCI-funded team led by investigators at Stanford University shrank pediatric tumors that were grafted into mice by priming T cells (one kind of immune cell) to recognize a protein called B7-H3 found on the surface of some pediatric cancer cells. More recently, NCI intramural researchers developed three cell therapies for adults that target the cancer cell markers GPC2 and mesothelin in mice and GPC3 in humans to treat neuroblastoma, lung cancer, and liver cancer, respectively. With a cancer-specific surface protein library in hand, researchers can explore how to target solid tumor cells more effectively.

While this is a promising area of research, there are more challenges to overcome. Further research is needed to identify who will benefit most from cell therapy and how to make a person's cancer more vulnerable to these treatments.

Studies to address these challenges are underway. In an NCI-funded first-in-human trial involving three participants with treatment-resistant cancer, researchers from the University of Pennsylvania and Stanford University School of Medicine genetically engineered T cells to recognize each patient's specific cancer and to ignore immune-suppressing signals coming from the tumors. The modified T cells were safe to use and persisted in humans, and they were able to target the tumors in each of the three patients.



Investing in a full set of tools for the cell therapy toolbox

In the same way that a tool is designed for specific functions, an immune cell is made for specific tasks. You would not use a hammer to turn a screw, and you would not use an immune cell that detects surface proteins to target a cancer cell's internal machinery. That is why we need to add multiple cell types to the cell therapy toolbox.

Chimeric antigen receptor (CAR) T cells have been a favorite for cell therapy applications and have been used in all FDA-approved cell therapies to date. However, other immune cells, including tumor-infiltrating lymphocytes (TILs) developed to treat melanoma and breast cancer, show promise.

Each approach has benefits but also challenges to overcome. Continued investments will help us optimize these approaches, learn which tools work best for each cancer type, and potentially add more cell types to the cell therapy toolbox.

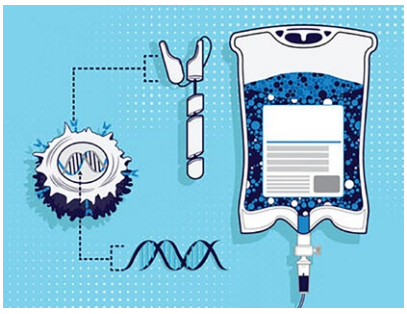
- **chimeric antigen receptor (CAR) T cells**: A patient's own T cells are modified in the lab with a receptor, called CAR, that is designed to recognize molecules, called antigens, on the surface of cancer cells. More research is needed to establish a library of tumor-specific antigen markers for every cancer type.
- **engineered T-cell receptor cells**: A patient's own T cells are engineered with a receptor that detects cancer-associated proteins that are processed inside the cancer cell and presented on its surface by a specialized protein complex. More research is needed to develop synthetic biology approaches that build safer, more effective, longer-lasting engineered T-cell receptor cells to treat solid tumors.
- **tumor-infiltrating lymphocytes (TILs)**: T cells that have already invaded a patient's tumor are removed and grown in large numbers in the laboratory to infuse back into the patient. More research is needed to overcome immune-suppressing signals so that TILs and all other cell therapies are more effective.
- **natural killer (NK) cells**: Like T cells, NK cells can be modified to express receptors that target the destruction of cancer cells. As their name implies, natural killer cells eliminate pathogens and abnormal cells. More research is needed to develop these newer cell therapy technologies and overcome early challenges, such as helping cells survive once reintroduced into the patient.

With more research, we can envision cell therapy approaches that are tailored to each cancer type. NCI's notable foray in this area is the NCI Center for Cell-Based Therapy, a Cancer Moonshot℠ project. The center is a multidisciplinary community within the NCI intramural program that facilitates and accelerates the further development of cutting-edge cell therapy approaches.

Boosting infrastructure support for rapid cell therapy advancements

NCI is making the infrastructure investments needed to establish cell therapy as a viable treatment option for more cancer types. For example, NCI will grow and promote the Cancer Adoptive Cellular Therapy Network (Can-ACT). This new network fills a significant gap in the research community: providing support for early-stage clinical testing of novel cell therapies for solid tumors in adults and children. To produce the cell therapies needed for these studies, the Frederick National Laboratory for Cancer Research offers standardized cell therapy manufacturing to researchers across the United States.

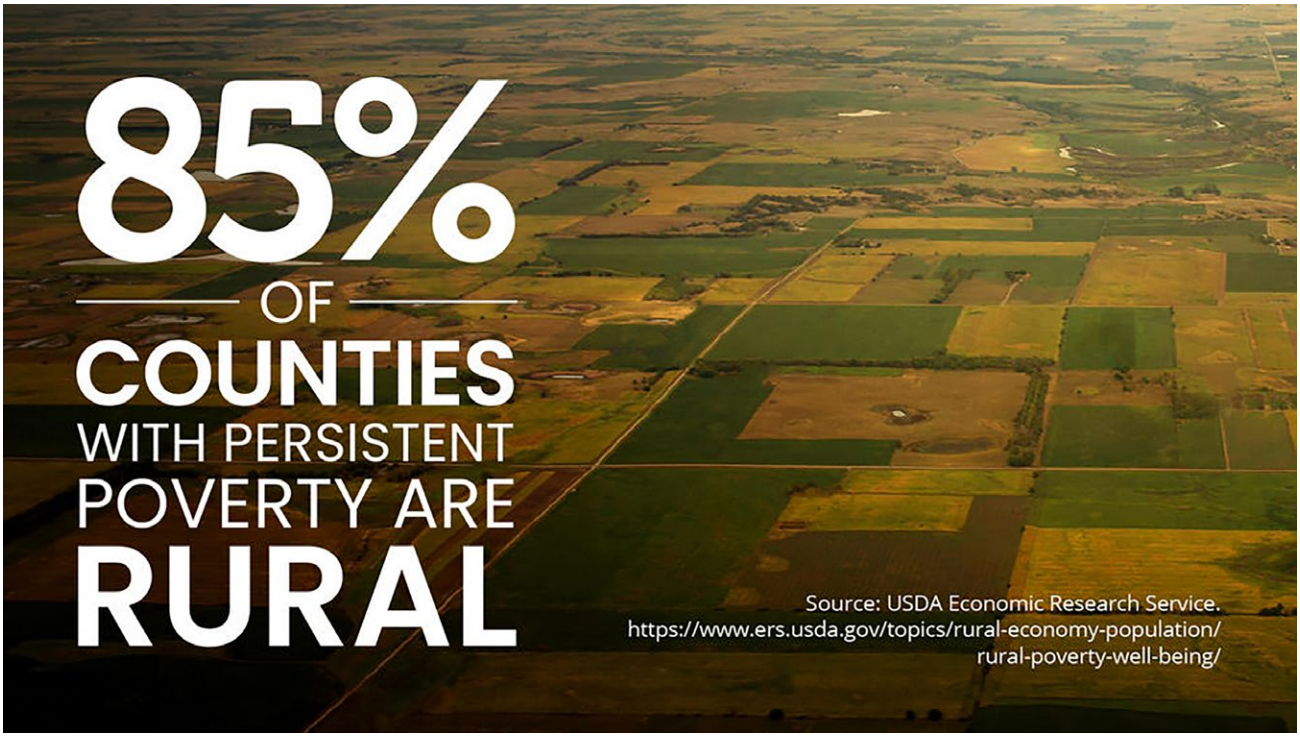
These NCI-supported resources are critical for meeting the technical and manufacturing challenges that cell therapy researchers face today. Sustained NCI support will help streamline cell construction technologies and develop standardized cell handling procedures. These processes are essential components to rapid and safe cell therapy production—and to a future where we can offer cell therapy to more patients.



NCI AIMS TO BOOST CAR T-CELL THERAPY CLINICAL TRIALS

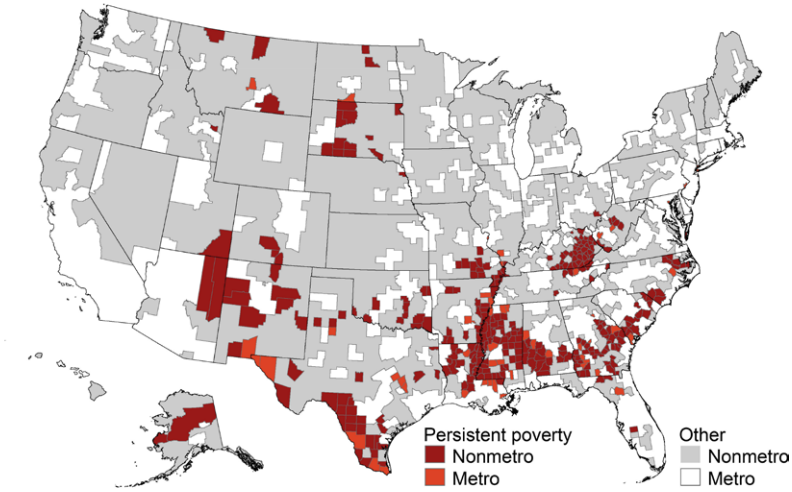
Initiative will manufacture therapies to be tested at multiple trial sites.

PERSISTENT POVERTY AND CANCER: INCREASING HEALTH EQUITY ACROSS THE CANCER CONTINUUM



As many as 16.5 million people in the United States live in counties with persistent poverty—areas where more than 20% of the population has lived below the poverty level for the past 30 years. Recent research has shown that death rates from cancer in counties with persistent poverty are 12% higher than in other US counties and 7% higher than in counties with more recently developed poverty. Without effective interventions, persistent poverty will continue to exacerbate health disparities in cancer and other diseases. This effect on cancer disparities is a multigenerational, population-level problem that requires institutional-level solutions.

Persistent poverty counties, 2015 edition



Persistent poverty counties are those where 20 percent or more of county residents were poor, measured by the 1980, 1990, 2000 censuses, and the 2007-11 American Community Survey.
Note that county boundaries are drawn for the persistent poverty counties only.
Source: USDA, Economic Research Service using data from U.S. Census Bureau.

Many counties with persistent poverty are clustered in the southeastern United States.

Credit: United States Department of Agriculture

Persistent poverty is defined as 20% or more of a county's population living below the established poverty level for the past 30 years.

NCI is supporting research into the multilevel and multifaceted nature of this problem. Those who live in persistent poverty areas are more likely to have greater exposure to cancer-causing and infectious agents, lack adequate housing, experience food scarcity and increased stress, and have poor access to transportation and health care. Adding to this complex situation, most persistent poverty areas have high concentrations of racial minorities who face additional burdens such as racism. NCI is funding research to understand how these factors intersect to affect cancer outcomes through cooperative agreement grants with those who live in persistent poverty areas, as well as through other funding mechanisms.

More research is needed to clarify the systemic causes of persistent poverty that lead to health disparities, and specifically the associations with higher rates of cancer death. Government agencies play a critical role in supporting these public health research programs. For example, NCI engages with other federal agencies, community members, and leaders to enable training and research opportunities that improve our understanding of health inequity's effect on cancer outcomes and to develop culturally appropriate interventions with communities in mind.

Peeling back cancer disparity's many layers

Research suggests that living in low-resource neighborhoods has a significant negative impact on health outcomes. For example, living in neighborhoods with lower income, education, employment, and housing quality is linked to worse survival among people with nonmetastatic breast, prostate, lung, and colorectal cancer. Similarly, the prognosis for people with ovarian cancer worsens relative to how poorly their neighborhoods score in these categories. These findings from NCI-supported research point to the influence of neighborhood poverty levels on individual cancer outcomes. When persistent poverty is factored in, the statistics worsen further.

In a pivotal study on cancer outcomes and persistent poverty, NCI-funded researchers from the Pennsylvania State University and NCI found that Black residents living in rural counties with persistent poverty had the highest rates of cancer death in the United States. This finding highlights the joint contributions of persistent poverty, rural environment, and race on cancer mortality. More research is needed to develop multilevel interventions that address the intersecting factors affecting a patient's risk of developing and dying from cancer.

Many more collaborative studies are needed. NCI plans to examine how persistent poverty impacts different populations, and this will require federal-level support to build trust in cancer research and evidence-based interventions within underserved communities. By identifying the traits that make populations in persistent poverty most vulnerable to high cancer death rates, we can begin to connect research findings with interventions and improve cancer outcomes for all patients.

Ending cancer disparities from persistent poverty through evidence-based decisions

The federal government plays an important role in collecting and storing cancer data for health equity research. The Surveillance, Epidemiology, and End Results (SEER) Program collects and publishes cancer incidence and survival data from population-based cancer registries in 19 US regions. This massive undertaking feeds other NCI-supported resources, such as the NCI Cancer Atlas, a free, interactive digital tool that allows users to access US cancer statistics by geographic area, race, gender, and cancer type. Our country's resources are best spent on evidence-based interventions, and more funding is needed to turn data into decisions that decrease the risk of cancer death for people living in communities with persistent poverty.

With new computer technology, researchers can dive into these high-quality data sets to tease out associations between community traits and cancer outcomes. For example, NCI-funded researchers analyzed SEER data using artificial intelligence software to understand what characteristics are associated with a late-stage breast cancer diagnosis. Their findings point to disparities in diagnosis among southern and western states caused by a lack of health insurance, low screening rates, poor socioeconomic status, and rural settings. More research is needed to make evidence-based decisions on how best to use local intervention programs to reduce cancer disparities.

Federally supported research, data collection, maintenance, and analysis are critical for population and community interventions to improve cancer outcomes. We can envision using high-quality data sets that link cancer outcomes, geographic areas, community traits, behavioral data, and biological data to inform comprehensive cancer care strategies for patients in communities with persistent poverty.

Beyond the individual: Addressing cancer disparities at the structural level

We can no longer focus on addressing cancer prevention and treatment solely at the individual level. Doctors encourage patients to eat right, exercise, and get routine cancer screenings, but we also need to implement structural-level prevention, care, and survivorship strategies that reach beyond the individual, into institutions and communities. NCI is committed to retooling how we think about population-level cancer disparities and tackling their causes at the structural level.

Part of NCI's efforts include supporting research programs that evaluate remote cancer care delivery to patients who live in rural communities with persistent poverty. For example, NCI-funded researchers at Vanderbilt-Ingram Cancer Center in Nashville, TN, are exploring telehealth-based interventions that give rural providers access to specialized expertise and that give their patients access to additional supportive care. Studies like this aim to identify potential strategies that can enhance the quality of cancer care delivery in areas of persistent poverty.

NCI has also provided funding to NCI-Designated Cancer Centers to conduct studies focused on building research capacity in impoverished areas. Researchers from Roswell Park Comprehensive Cancer Center are creating community–clinic partnerships as part of cancer disparity research programs built in impoverished, rural African-American counties in Arkansas. Additionally, researchers from Vanderbilt University Medical Center are using NCI support to build capacity and bring cancer research efforts directly to areas of persistent poverty in the South.

Through these studies, NCI is taking a community-based approach to build trust among populations that have traditionally been underserved. Greater investments, however, are needed to build this trust. NCI support will enable the research community to tailor their approaches and methodologies to this community-based, population-level challenge. From these efforts, we can imagine comprehensive cancer interventions that reach and are accepted by all communities, no matter the zip code. NCI is well suited to design and implement this more inclusive model of cancer care.

UNDRUGGABLE CANCER TARGETS: TACKLING DIFFICULT DRUG DESIGN

Hundreds of different types of cancer occur in humans, but they all have one thing in common. Every cancer cell contains alterations that lead to the production of abnormal proteins responsible for uncontrolled cell growth and survival. Many precision cancer medicines block the activity of these abnormal proteins by binding to them. However, there are cancer-driving proteins that have eluded all attempts to stop their harmful effects. For years, researchers have struggled to develop treatments that work on these so-called "undruggable" targets. Frequently, the pharmaceutical industry has considered them too risky to explore, but NCI has long supported this research.

Over the past 5 to 10 years, NCI-funded researchers have developed new strategies to tackle these difficult targets thanks to advances in chemistry, computational approaches, and imaging coupled with a deeper understanding of cancer biology. For example, in 2021, the Food and Drug Administration (FDA) approved the first drug targeting a mutated form of a protein called KRAS. Finding a drug to target KRAS, one of the most frequently mutated drivers in cancer, is a celebrated milestone that provides new proof of principle for future drug development.

Armed with novel tools and more knowledge about cancer biology than ever before, researchers have made significant progress developing ways to target previously undruggable cancer drivers. NCI support has contributed to research on degrading cancer-driving proteins (an alternative to blocking their activity), manipulating interactions between interdependent proteins, and targeting nonprotein cancer-driving molecules. However, a substantial number of important proteins have yet to be targeted successfully, and a full understanding of all potential therapeutic targets in cancer remains elusive.

Sustained investment is needed to seize on the progress that has been made so far—from foundational discoveries to new tools and technologies. Spurred by recent advances in drug design, we are approaching a point where very few cancer drivers may be considered "undruggable." Getting to that point could result in strategies to target almost any abnormal protein and medicines for more patients.

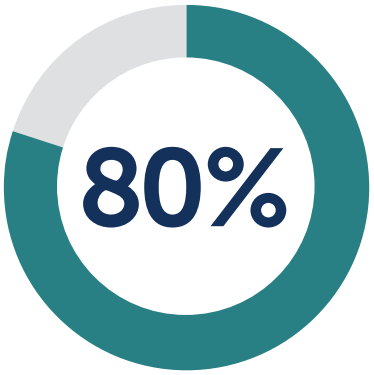
Leveraging basic research for successful drug design

NCI has a long history of supporting discovery science—the type of fundamental research that leads to novel approaches to cancer treatment. One shining example of this is support that ultimately led to the development of sotorasib (Lumakras), an FDA-approved drug for non-small cell lung cancer. The success of sotorasib is grounded in years of NCI-funded basic research in structural biology and chemistry.

Sotorasib is a small molecule that irreversibly binds to KRAS proteins, which are one of the most prevalent drivers of non-small cell lung cancers and can cause unrestrained cell growth when mutated. After a series of breakthrough studies on KRAS protein structure, supported in part by the NCI-funded RAS Initiative, researchers keyed in on the unique ability of sotorasib to lock KRAS in its inactive form when it harbors a specific alteration. A subsequent clinical trial showed that sotorasib controlled non-small cell lung cancer in about 80% of patients with the relevant *KRAS* mutation.

DRUGGING THE UNDRUGGABLE

A CLINICAL TRIAL SHOWED THAT
SOTORASIB CONTROLLED NON-SMALL CELL LUNG CANCER
IN ABOUT



OF PATIENTS WITH THE G12C
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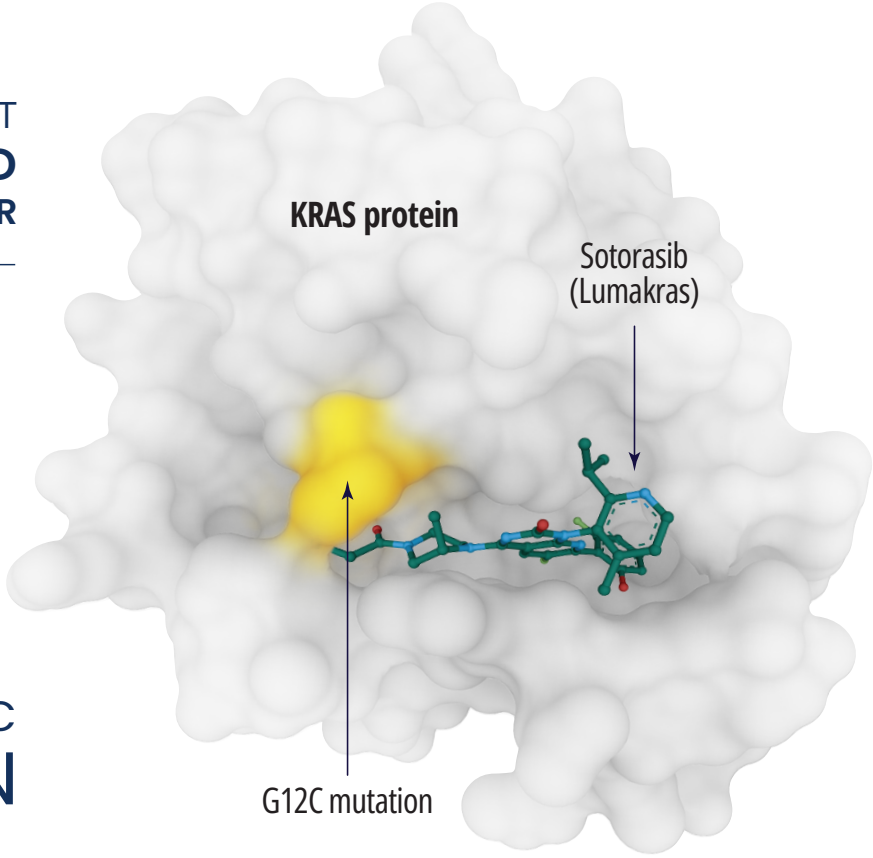


Space-filling model of human KRAS bound to sotorasib

Sources: Skoulidis F, et al. doi: 10.1056/NEJMoa2103695
Sehnal D, et al. doi: 10.1093/nar/gkab314

This exciting work serves as a launchpad for new ways to target proteins that develop resistance to available targeted therapies. For example, cancers treated with drugs that target abnormal EGFR proteins, another prevalent cancer driver, are prone to developing drug resistance. While the EGFR-targeting drugs initially treat the cancer, in many cases the drugs ultimately lose their effectiveness as resistant forms of abnormal EGFR arise, rendering EGFR undruggable in the patient. NCI-supported researchers have found preliminary success by locking abnormal forms of the EGFR protein into an inactive shape, like researchers did for KRAS.

NCI sustains the sort of infrastructure that powers this type of success. For example, researchers need access to cutting-edge microscopy to generate high-quality protein structures, and they need data to be made publicly available for others to use. Federal programs bolster access to these resources for the scientific community, including for researchers and institutions that lack their own infrastructure for this critical work.

Discovering RNA as a drug target and a potential drug

Supported by growing genomic databases and the advent of fast, inexpensive genetic engineering technology, NCI-supported researchers are broadening their scope beyond proteins and into RNA-based drug design. Our knowledge of the various types of RNA continues to expand. One type of RNA is an intermediary molecule that helps convert DNA instructions into proteins, a tempting target to prevent the effects of harmful gene alterations. Other types of RNA regulate basic functions in the cell.

New RNA-targeting drug strategies deepen the pool of druggable targets in cancer cells. In one study, NCI researchers discovered a natural product that binds cancer-driving microRNAs, a specific type of RNA product, and stops colon cancer cells from multiplying in a petri dish. This preliminary study sets the stage to investigate RNA-targeting drugs further, but more research is needed to understand all RNA alterations and druggable features in cancer cells.

Some researchers are using RNA as the drug itself. NCI-supported scientists from the Fred Hutchinson Cancer Research Center and Memorial Sloan Kettering Cancer Center created a synthetic RNA that makes cancer cells vulnerable to the drug ganciclovir (Zirgan). Their approach worked in mice implanted with leukemia, uveal melanoma, and breast cancer cells that shared a specific RNA-processing mutation. With more synthetic RNA research, we can imagine treatment options that could multiply the number of cancer drugs available to patients.

Driving innovative cancer drug design with cutting-edge technologies

Federal support is vital to new drug development—whether those drugs target proteins, RNA, or other cell components—since industry is reluctant to pursue this type of foundational research until proof of principle is established. Several exciting developments are playing out in NCI-supported laboratories around the country.

For example, researchers are exploring nanomaterials that can detect cancer byproducts in body fluids, visualize cancer cells in the body, and deliver drugs directly to the cancer cells. In one study, NCI-supported researchers at the Washington University School of Medicine in St. Louis treated aggressive metastatic breast cancer in mice using nanotechnology to activate drugs at the site of cancer cells only, reducing toxic side effects on healthy cells.

Other NCI-supported researchers are finding new and better ways to link molecules together to design more effective cancer drugs. This includes linking drugs to cancer-seeking antibodies or creating bifunctional molecules that can both find and destroy cancer-driving proteins. Bolstering these technological advancements could lead to an entirely new class of highly targeted cancer treatments and shrink the list of undruggable proteins.

One cutting-edge approach that has received notable attention from both academic researchers and the pharmaceutical industry is proteolysis targeting chimeras (PROTACs), which are bifunctional molecules that bind cancer-driving proteins and target them for destruction. Early efforts have culminated in the development of the first clinical agents of this class targeting solid tumors. This technology has also inspired a tidal wave of

interest in the development of small molecule degraders using this approach, as well as "molecular glues" that hold together two proteins that wouldn't normally interact.

More recently, NCI-supported researchers have successfully used PROTAC technology to suppress tumor growth in animals by targeting the otherwise hard-to-block EZH2 protein, which has been linked to cancer progression and poor survival. These early results suggest PROTACs offer great promise. However, developing effective PROTAC molecules is challenging, and more federal support is needed to further refine this cutting-edge technology.

Now imagine taking decades of information about cancer biology and drug design and using computers to predict the most efficient cancer drugs. Computational biology researchers are doing just that. Continued federal support for computer-based drug design is critical to develop and maintain the type of computational power and data sets needed for drug design analysis. Investments in computational capability have the potential to impact all areas of drug design and lead to novel pharmaceutical approaches that could make a major impact on ending cancer as we know it.

BRINGING CANCER PREVENTION TOOLS TO UNDERSERVED COMMUNITIES

Experiences that Jennifer Moss, Ph.D., from Penn State College of Medicine, had as a child, while living in a variety of states and communities, showed her that where people live can influence their health. As the first in her family to attend college, she received a fellowship with an organization that focused on underserved and underrepresented students. This led to a bachelor's degree in psychology and graduate studies in health behavior.

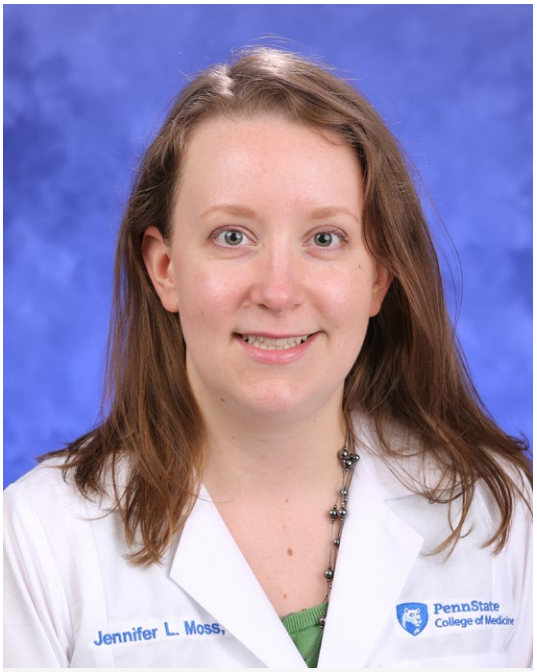
Jennifer whittled down her broad interest in women's health to focus on human papillomavirus (HPV) vaccination research, cervical cancer burden, and cancer prevention tools. Encouraged by advisers and mentors, Jennifer applied for and received training support from NCI that included a Cancer Prevention Fellowship nestled between her predoctoral F31 and current postdoctoral K22 grants.

Persistent poverty, cancer, and the rural environment

It was during the NCI prevention fellowship that Jennifer worked on a study of cancer outcomes in US counties, which was the first to examine how persistent poverty, rural environment, and race work together to produce higher rates of cancer death. The study concluded that multilevel interventions addressing these issues are needed to improve cancer outcomes.

The research solidified Jennifer's interest in the impact of geography on health outcomes in rural areas. "We know we can prevent up to 50% of cancer mortality through behavior change. But it's hard to change people's behavior—health-related behaviors in particular," she reflected. In counties with persistent poverty—of which 85% are rural—creativity is paramount. "These aren't communities that have a lot of resources that you can connect people with to enhance their health. You have to think more creatively about how to use community assets that are a little less traditional, like churches and community groups."

Jennifer's research has shown that a one-size-fits-all approach is often ineffective. "Rural communities are different from each other," Jennifer explained. "Understanding the differences across rural communities that make people more or less likely to get and die from cancer is not only helpful for rural populations, but for the whole country." She hopes her research will help identify factors that give rise to the burden of cancer disparities.



With a postdoctoral grant (K22) from NCI, Jennifer is studying the effect of educating women in rural, segregated communities about cancer screening, specifically for cervical and colon cancers.

Credit: Headshot courtesy of Jennifer

PERSISTENT POVERTY AND CANCER: INCREASING HEALTH EQUITY

NCI is supporting research to clarify systemic traits of persistent poverty that lead to cancer disparities.

Bringing cancer prevention tools to the underserved

Patients in the rural communities of Pennsylvania where Jennifer works often have limited access to health care services. She collaborates with health centers to get people the clinical cancer prevention services they need. Specifically, Jennifer's postdoctoral K22 grant studies the effect of providing eligible women in rural, segregated communities with educational materials about cancer screening and self-collected cervical (HPV) and colorectal (fecal immunochemical test [FIT]) cancer screening tests.

More than 70% of eligible participants in her study have completed self-sampling tests. She's elated with this success rate. "Many people have said, 'I'm so glad to help you figure this out. And I want to help other people who are like me,'" Jennifer said. "They've told us about talking with their partners, their parents, their children—it's opened up conversations about what everyone in the family can do to reduce the risk of cancer."

Support for innovative research

Jennifer is grateful for NCI's support. "I can't overstate the positive impact that NCI has had on my career. It's allowed me to do innovative research, work with a number of exciting collaborators, and reach out to patients who are often left out of scientific work," she said. Recently, she received a supplement to her K22 award that supports the continuation of her research while she is on maternity leave. This serves as an example of how NCI supports early-career investigators.

For Jennifer, NCI's support has allowed her "to focus on making sure my science is as good as possible—rigorous, innovative, and impactful—as I try to make a difference in people's lives and decrease the cancer burden in this country."

CHANGING THE LIFE OF A PATIENT WITH VON HIPPEL-LINDAU SYNDROME

When he was 6 years old, Justin was diagnosed with von Hippel-Lindau (VHL) syndrome, a rare inherited disorder that increases the risk of developing noncancerous and cancerous tumors in multiple organs.

For more than a decade, Justin was in and out of hospitals, undergoing kidney, adrenal gland, spinal, and brain surgeries—more than a dozen operations by the time he entered his 30s. Many of these procedures were performed at the NIH Clinical Center in Bethesda, MD, where he and his family have been participating in a natural history study of VHL since the mid-1990s. Justin knew he was facing a routine of cancer surveillance tests, surgery, and physical therapy for the rest of his life.

Managing VHL involves frequent body scans to look for and monitor tumors, along with surgical interventions to treat symptoms and prevent cancer from spreading. Doctors typically perform surgery when tumors grow to a size that increases the risk of metastatic spread and may begin to affect the function of organs. Each successive surgery increases the risk of complications.

Justin's dad, from whom he inherited VHL, had walked a similar path. "A lot of my youth revolved around seeing my dad go in and out of hospitals," Justin recalled. "Since my father's diagnosis in 1989, his life was basically one surgery after another." A week before Justin's 30th birthday in 2016, his dad passed away. Justin credits his dad's will to fight VHL for so many years as an inspiration.

Justin, a patient with von Hippel-Lindau syndrome, decided to join a phase 2 NCI trial of belzutifan, and it changed his life.

Credit: Headshot courtesy of Justin

Gambling on a new drug

When Justin experienced terrible symptoms a few years after his dad's death, his doctors at the NIH Clinical Center found multiple tumors that needed to be addressed. Justin's recollection is that picking which one to remove to reduce his symptoms would be a gamble. Instead, his doctors encouraged him to enroll in a clinical trial testing a new targeted therapy, now known as belzutifan (Welireg). Justin initially declined but later decided to enroll in the trial.

NCI researchers pioneered the research that ultimately led to the development of belzutifan. In the early 1990s, they identified the VHL gene, which is mutated in people with the syndrome. This identification and understanding of the VHL gene enabled the development of the targeted therapy.

Justin's gamble to join a phase 2 trial of belzutifan changed his life. The tumors stopped growing, and he has not had a surgery since. The relatively mild side effects from the daily pill and less frequent scans are worth it.

UNDRUGGABLE CANCER TARGETS: TACKLING DIFFICULT DRUG DESIGN

NCI supports research to drug cancer's undruggable targets.

A few years after starting treatment, Justin felt well enough to travel to Japan and Taiwan, where he met his wife. “With all the surgeries, I never had the chance to go out and explore. I was stuck in a hospital room. Belzutifan allowed me to travel internationally,” he said. “And if it wasn’t for the drug, I probably would’ve never gotten married.” He now envisions a future with children and more trips to Asia—and a special goal to visit Rome by age 40.

Becoming a new standard-of-care treatment

In August 2021, the Food and Drug Administration (FDA) approved belzutifan to treat several types of VHL-associated tumors. The approval was based on the results of the phase 2 trials conducted by NCI researchers and others.

“This is the first time we have an FDA-approved agent for the treatment of patients with VHL-associated tumors,” said Justin’s doctor, Ramaprasad Srinivasan, M.D., Ph.D. “Now we can say to some patients, ‘We can give you a drug that may help you avoid surgery.’”

NCI researchers continue to study the drug to better understand its effect on tumors and its long-term use with surgery. With more research, they hope that belzutifan will be approved for other VHL-associated tumors.

In the spring of 2022, Justin’s older brother, who also was diagnosed with VHL in childhood, was able to start belzutifan. The brothers hope that the drug will be as effective for him as it has been for Justin. “Without NIH, I probably wouldn’t be alive,” Justin said. “For the first time in my life, I find myself looking forward to what the future holds for me.” He wants the same for his brother and others with VHL.

EXPERIMENTING WITH HOPE: HOW CANCER RESEARCH SAVED EMILY'S LIFE

Emily Whitehead had just celebrated her 5th birthday in 2010 when she was diagnosed with acute lymphoblastic leukemia (ALL). More than 90% of children diagnosed with ALL are cured, but Emily relapsed twice. In April 2012, her parents, Tom and Kari, were told she had no more options. "It got to where Kari had to stop doing research [on treatments], because [it] showed Emily wasn't going to survive," said Tom. But, said Kari, "I thought, 'this can't be it. There has to be something else we can try.'"

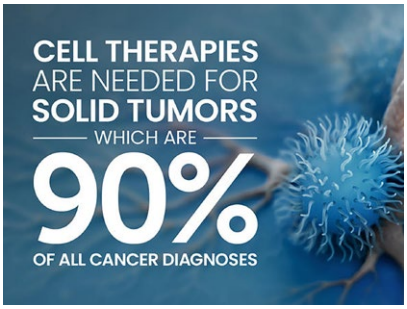
From left: Tom, Emily, and Kari Whitehead. Nine years ago, Emily was the first child in the world to receive CAR T-cell therapy.

Credit: National Cancer Institute

Children's Hospital of Philadelphia was running a clinical trial studying CAR T-cell therapy, which takes a patient's T cells (a type of white blood cell) and genetically modifies them to attack their cancer. When Tom and Kari found out about the trial, they didn't hesitate to enroll Emily. "Some parents would think, 'I'm not sure I want my child to be a science experiment,' but trying these experimental studies is what leads to breakthroughs," said Tom.

Emily was the first child to receive CAR T-cell therapy, and in May 2012—23 days after treatment—there was no cancer in her body. It has never returned. Inspired by their daughter's recovery and the potential for this research to help other children, the Whiteheads launched the Emily Whitehead Foundation. Through the foundation, they've supported other families, funded research, and helped get the first CAR T-cell therapy approved by the FDA, making it more accessible to patients worldwide.

"My favorite part of our work is that we help families find better treatment options for their child fighting cancer," said Emily, "So the child can have a more normal childhood and spend less time in the hospital." Nine years cancer free, high schooler Emily enjoys playing with her chihuahua, Luna, painting, photography, and reading, and she wants to go to film school. A breakthrough in cancer treatment allowed her to be a kid again, and now she's traveling the world to increase awareness of childhood cancer and the therapy that saved her life.



CELL THERAPY: HARNESSING IMMUNE CELLS TO FIGHT CANCER

NCI-supported cell therapy research aims to expand this treatment to more people with cancer.

IT TAKES A VILLAGE—HELPING THE VULNERABLE NAVIGATE CANCER

They see around 12,000 patients combined a month, many underserved. It's challenging but rewarding work for the folks at Pittsburgh's UPMC Hillman Cancer Center and Birmingham Free Clinic. Dr. Linda Robertson (Lyn), Patricia Andres-Sanmartin (Patty), and Lilcelia Williams (CeCe) are part of a network connecting underserved patients with cancer screenings, clinical trials, and other programs to support their health journeys.

Patricia Andres-Sanmartin, Lilcelia Williams, and Dr. Linda Robertson connect people in underserved communities in Pittsburgh, PA, with screening programs and clinical trials.

Credit: National Cancer Institute

For Patty, a Spanish interpreter and patient navigator at Birmingham, language access is especially crucial. "What good is it to have the most wonderful doctor giving the best advice if you don't understand it?" she said, adding that patients who are elderly, uninsured, immigrants, or non-English speakers can get overwhelmed by the health care system. She's driven to help because "if we have screening programs and patients who need them but don't connect the two, they go to waste."

While clinical trials can be a viable treatment option, patients of color may still feel apprehensive. As a research specialist, CeCe emphasizes the protections in place for trial participants and discusses how "participation is important now and can lead to better outcomes for our children and grandchildren." Regardless, she said, "the patient is the expert of their body. They are in control. We're here to guide them but also support them with whatever they decide."

Lyn, an associate director at Hillman, echoes this message of support and education. "People think being in a clinical trial means getting a placebo or going off treatment," but that's not the case, she said. "We're constantly breaking down what a trial is, what types there are, and why we call them the gold standard of care" through community sessions or even games. "Many communities know us and trust us, but it takes time to achieve that."

When asked what motivates them, each of these women lit up and said, "the patients," who they also help with necessities like securing housing or food. Witnessing and addressing barriers to care can be frustrating, but this team remains dedicated to being there for whoever needs them.