Annual Plan & Budget Proposal for Fiscal Year 2023
Table of Contents

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— At a Glance —

DIRECTOR'S MESSAGE: IT'S TIME TO END CANCER AS WE KNOW IT

In the 50 years since the National Cancer Act of 1971 was signed into law, we have made remarkable progress in cancer research. Cancer death rates have declined 31% since their peak in 1991. In fact, the rate of decline has accelerated in recent years. We've also seen record numbers of Food and Drug Administration approvals for cancer treatments emerge from decades of fundamental research and exciting new technologies that have created new opportunities across the spectrum, from prevention to diagnosis to treatment to survivorship. Even COVID-19 could not stop us.

These advances have led us into a golden age of cancer research. If we harness the promise of this golden age, we can end cancer as we know it. This means transforming the tragedy of cancer, especially in younger and otherwise healthy people. A major step on our path toward this goal would be to cut the cancer death rate in half from its peak in the 1990s. I believe we will do this, and I believe we'll get there soon.

It has been the National Cancer Institute's work to create the structures that enable this progress, and our current work is poised to accelerate the pace of research progress. Progress-enabling efforts take many forms and include supporting foundational basic research, training the next generation of cancer

Norman E. Sharpless, M.D., NCI Director

caregivers and researchers, and providing the data infrastructure and data sets needed for research. NCI also works across the federal government to support the development of policies that support cancer care and research.

Examples of key infrastructure include the Cancer Research Data Commons and Childhood Cancer Data Initiative. These linked efforts offer access to clinical and molecular data and research tools that have unleashed opportunities for studies that were never possible before. In addition, the Cancer Moonshot℠ has enabled us to create interdisciplinary teams that work together to lead and spread the reach of cutting-edge research, such as immunotherapy approaches for children and adults. With Cancer Moonshot funding drawing to a close at the end of fiscal year (FY) 2023, we will look for ways to sustain this bold effort that has accelerated progress in cancer research.

To end cancer as we know it will require sustained strong investments and team-based efforts. Advances in our understanding and treatment of cancer are built on foundational research, which is largely supported through grants for investigator-initiated projects. It is therefore essential that NCI achieves its goal to increase the fraction of applications that can be funded to the top 15th percentile of R01 applications by FY 2025. Research project grants, including R01 grants, are the source of some of the most innovative and transformative ideas in cancer research. This investment would increase the number of meritorious research proposals NCI funds and ensure that we take advantage of the recent boom in applications from new investigators entering the field.

Without robust and sustained budget increases, paylines cannot be raised, and we would miss out on many great ideas that could advance cancer research.

President Biden's goal is to end cancer as we know it for all Americans, regardless of race, ethnicity, or income. To achieve this, NCI is fully committed to promoting health equity in all our work. We will ramp up our efforts to grow a more diverse and inclusive cancer research workforce and foster a culture in which everyone flourishes. NCI has long been a leader in supporting research on cancer disparities, and we will build on that strong tradition to ensure that reducing disparities remains a priority throughout our research.

VCU Massey Cancer Center's Dr. Vanessa Sheppard, a cancer survivor and researcher highlighted in this *Annual Plan & Budget Proposal*, typifies the kind of researchers we believe will help us overcome cancer disparities. She champions the approach that "we must embed community voices in what we do" and that through dialogue we can increase much-needed cancer screenings and clinical trial participation in these communities.

Looking to the future, we have highlighted four scientific opportunities in this *Annual Plan & Budget Proposal* that would greatly accelerate progress:

- For people with cancer, participating in a clinical trial should offer hope, not additional burdens to bear. We have the opportunity to bring clinical trials to more people, no matter where they live, by making it possible for them to enroll in their own communities and by using the latest technology, including telemedicine.
- Far too many people face cancers for which there are no effective treatments. Computer-based drug design could dramatically speed up drug discovery and, ultimately, help shorten the 10 to 15 years it typically takes for a new medicine to complete its journey from initial discovery to patient benefit.
- Precision prevention offers the promise of personalized prevention and screening approaches tailored to a person's individual cancer risk based on their genetic makeup, family history, environmental exposures, and behavioral factors.
- The staggering complexity of tumors makes it difficult to predict how a person's cancer will progress or respond to treatment. We plan to use the latest technologies, such as artificial intelligence, to enhance the study of tumor dynamics to help learn why some tumors evolve into malignant cancers, how they progress, and why they either respond to or resist therapy.

The proposed Advanced Research Projects Agency for Health (ARPA-H) would be a great partner to help realize the scientific opportunities before us. Pairing NCI's world-class basic and translational research expertise with ARPA-H's envisioned capability to foster rapid innovation at unprecedented scale would surely save more lives.

Thanks to the progress we have achieved since the National Cancer Act of 1971, the hope of ending cancer as we know it may finally be within our reach—not just for a few, or even many, but for *all* people. Because of the hard work and dedication of researchers and clinicians like Dr. Sheppard, continued support from Congress, and our partnership with patients, survivors, and their loved ones, I know we can achieve our goal.

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

SCIENTIFIC OPPORTUNITIES

NCI drives advances in cancer by investing in a broad portfolio of research, from basic science to survivorship. In addition to supporting 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 more progress in cancer research.

CLINICAL TRIALS

Ending cancer as we know it means reimagining the clinical trial enterprise so that clinical research is available to participants wherever they are. With additional investments, NCI can support more research to expand telemedicine into clinical trials, increase access to trials for underserved communities, and incorporate methods that simplify enrollment and data collection.

COMPUTER-BASED DRUG DESIGN

A future with safe and effective medicines that are available for every patient would end cancer as we know it. Additional investments in computational methods that rapidly screen billions of molecules for targeted interactions could speed drug discovery dramatically. This approach could produce a greater number of cancer drugs that work more effectively to save lives with fewer toxic side effects.

PRECISION PREVENTION

A precision approach to prevention could end cancer as we know it by limiting suffering and death for those at risk and helping others avoid unnecessary tests and treatments. Imagine determining a person's cancer risk by assessing their genetic makeup, family history, environmental exposures, and behaviors and then tailoring personalized prevention approaches based on these factors. Accomplishing this goal requires a deeper understanding of the causes of cancer and cancer biology.

TUMOR DYNAMICS

Ending cancer as we know it includes a future in which we can predict a tumor's trajectory based on a detailed profile of each patient's disease and develop personalized approaches to care. Addressing the complexity of cancer will require additional investments in basic research, coupled with resources including tumor atlases and advances in computer science and molecular techniques.

KEY MESSAGES

NCI is committed to investigator-initiated research.

The FY 2023 budget proposal would enable NCI to increase R01 paylines to the 13th percentile, allowing NCI to fund a greater number of meritorious applications. Robust and sustained investments are needed to achieve the 15th percentile R01 payline by FY 2025.

NCI is seizing new opportunities in cancer research and building on progress in established areas.

Beyond NCI's broad research portfolio, opportunities include expanding access to clinical trials, improving cancer drug design, understanding tumor dynamics, and advancing precision prevention. In addition to funding research project grants, investments are needed across a multitude of programs, including the NCI-Designated Cancer Centers and clinical trials networks that help translate scientific discoveries into new approaches for patients.

NCI's goal is to make health equity a priority in everything we do.

NCI will ramp up its commitment to building a diverse and inclusive cancer research workforce and support disparities research to ensure advances in cancer research benefit all people.

NCI seeks to sustain and leverage the unprecedented opportunities and progress created by the Cancer Moonshot once funding ends after FY 2023.

In its 7 years, the Cancer Moonshot will have initiated many new networks and established an infrastructure to conduct cancer research and share resources on a massive scale.

PROFESSIONAL JUDGMENT BUDGET PROPOSAL FOR FISCAL YEAR 2023
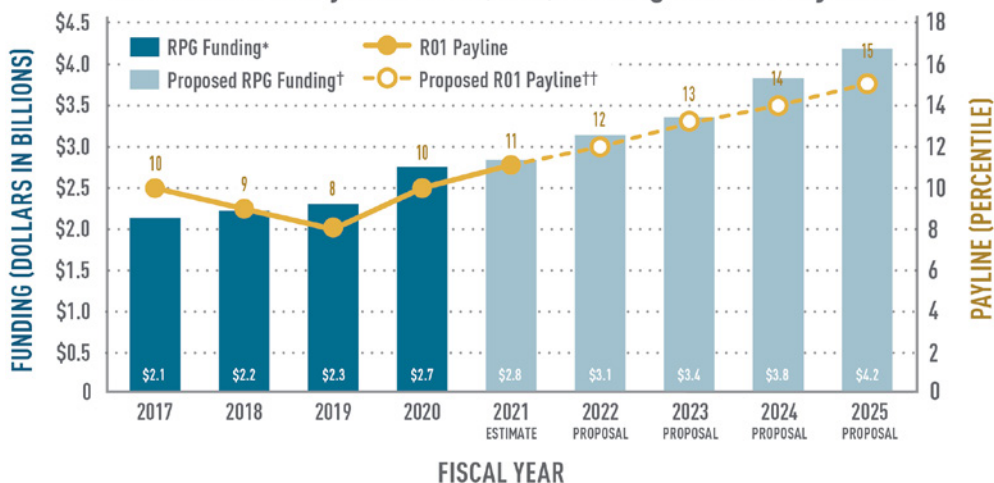
(DOLLARS IN MILLIONS)

FISCAL YEAR 2021 NCI BASE APPROPRIATION	**$6,365***		
TOTAL BUDGET INCREASE (Proposed Allocation)	**$1,185†**	$277	Inflation Adjustment††
		$165	Cancer Biology Research
		$185	Cancer Prevention Research
		$150	Cancer Detection & Diagnosis Research
		$205	Cancer Treatment Research
		$125	Public Health & Cancer Control Research
		$78	Training & Infrastructure
FY 2023 BUDGET RECOMMENDATION	**$7,550**		
FY 2023 CANCER MOONSHOT℠ FUNDING	**$216**		
FY 2023 TOTAL	**$7,766**		

* The base appropriation includes $50 million for the 4th year of the Childhood Cancer Data Initiative, a 10-year initiative that began in FY 2020.
† The increase of $1,185 million includes an inflation adjustment and $908 million for additional infrastructure and cancer research in six major focus areas.
†† This adjustment includes inflation for the 2 years between FY 2021 and FY 2023.

NCI Research Project Grants (RPG) Funding and R01 Paylines

Legend: RPG Funding*, Proposed RPG Funding†, R01 Payline, Proposed R01 Payline††

Fiscal Year	RPG Funding	R01 Payline
2017	$2.1	10
2018	$2.2	9
2019	$2.3	8
2020	$2.7	10
2021 ESTIMATE	$2.8	11
2022 PROPOSAL	$3.1	12
2023 PROPOSAL	$3.4	13
2024 PROPOSAL	$3.8	14
2025 PROPOSAL	$4.2	15

* RPG funding levels include program evaluation and Small Business Innovation Research.
† FY 2021 reflects an estimate, and FY 2022 through FY 2025 are proposed professional judgment budget levels. Estimates beyond FY 2020 are subject to change due to unanticipated inflation rates, average cost increases, and fluctuations in application rates as the country recovers from the COVID-19 pandemic.
†† R01 paylines for FY 2022 through FY 2025 are proposed levels based on estimated funding levels included in this professional judgment budget.

With cancer research that spans the continuum from basic science to survivorship, we have an incredible opportunity to greatly reduce the impact of cancer on people's lives and end cancer as we know it. This budget proposal for FY 2023 invests in the cutting-edge research, infrastructure, and training needed to harness these opportunities so that researchers better understand how to prevent and treat cancer.

This budget proposal advances progress toward NCI's goal of increasing the payline—that is, the percentile of applications NCI can fund—for research project grants (RPGs) and expands opportunities for early-stage investigators. The proposal also includes $50 million for the Childhood Cancer Data Initiative and $216 million for the final dedicated year of Cancer Moonshot funding.

Beyond funding for RPGs, some of NCI's other key investments include: the NCI-Designated Cancer Centers, the Specialized Programs of Research Excellence (SPOREs), and practice-changing clinical trial programs that enroll patients at over 2,500 academic and community sites across the country.

Across all our programs, NCI will make it a priority to address cancer disparities and grow a more diverse and inclusive cancer research workforce.

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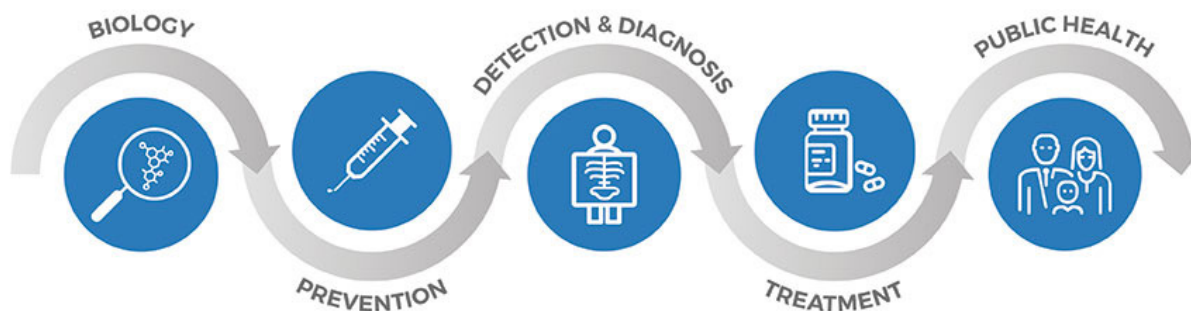
NCI enables advances in cancer by investing in a broad portfolio of research, supporting the cancer research workforce, and sustaining the infrastructure that enables cutting-edge research to succeed.

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.

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 that 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.

A Cancer Research Career Sparked by a Diagnosis of Her Own

AnnaLynn—St. Jude Children's Research Hospital, Tennessee

CLINICAL TRIALS: BRINGING CANCER RESEARCH TO ALL POSSIBLE PARTICIPANTS

The COVID-19 pandemic accelerated the use of virtual interactions between health care providers and patients. Researchers conducting clinical trials also increased their adoption of telemedicine, which helped NCI-supported clinical trial enrollment rebound from a 40% drop early in the pandemic to 80% of prepandemic levels. Researchers now hope to use the telemedicine experience gained during the pandemic to improve cancer clinical trials moving forward.

> A clinical trial is a research study done in people that helps health care providers understand the best approach to prevent, diagnose, treat, or manage symptoms of diseases, including cancer. Clinical trials can be used to evaluate a wide range of biomedical (e.g., treatment) and behavioral (e.g., exercise and diet) interventions. Clinical trials are the cornerstone of creating new cancer interventions and improving patient outcomes.

NCI supports clinical trials at over 2,200 sites throughout the United States and around the world through networks such as NCI's National Clinical Trials Network (NCTN), the NCI Community Oncology Research Program (NCORP), and others. These networks provide patients with access to highly trained scientists and physicians who study how to better prevent and treat cancer through carefully designed research studies. In addition, NCI funds clinical trials conducted by individual investigators or investigative teams.

While many companies and institutions around the world conduct cancer clinical trials to test new treatments, NCI also focuses on studies that industry does not. These include cancer prevention trials, trials testing behavioral interventions for cancer risk factors like smoking and obesity, de-escalation trials testing the effectiveness of using less treatment, and complex combination therapy trials using novel adaptive designs.

Clinical trials advance cancer prevention, screening, treatment, and survivorship, but challenges in planning and conducting clinical trials hinder even more progress for patients. For example, only a small percentage of all adults with cancer participate in clinical trials, and trials often do not adequately represent minority and underserved populations. This may lead to study results that fail to reflect health outcomes for the broad population with cancer. There are additional hurdles for pediatric patients due to the rarity of childhood cancers and the additional support children and families need throughout the trial process.

Added challenges include the exponential growth in complexity and expense associated with cancer clinical trials. Extensive and complex data collection imposes burdens on everyone involved in a clinical trial and is a major contributor to the cost of conducting clinical trials.

Clinical trial innovations that break down barriers to participation and simplify study design are on the horizon. In 2020, NCI released a strategic vision for clinical trials that conceives of a future in which clinical trials are flexible, faster, simpler, less expensive, more equitable, and higher impact. With additional research investments, the clinical trial enterprise will be able to:

- expand the use of telemedicine in clinical trials

- increase trial access for minority and underserved communities

- incorporate new enrollment and data collection approaches using modern, digital technology

- determine more quickly if a new intervention provides benefits to patients

Ending cancer as we know it includes reimagining the clinical trial enterprise so that clinical research is available to participants wherever they are. Participating in a clinical trial should bring hope for the future, not additional burdens to bear. Imagine joining a trial from your home or having your health monitored for a trial via wearable technology. There would be no need to take time off from work or travel to distant cities. With additional resources and collaboration, NCI has an opportunity to lead changes that will take advantage of the most compelling new scientific opportunities while assuring that the research benefits will be made available to all.

Leveraging the Power of Technology to Reach Patients Where They Live

Reaching participants in their communities will increase clinical trial access. Integrating telemedicine into clinical trials allows participants to talk to trial physicians or their health care providers without the added time and costs of traveling to a clinical trial site. To ease additional burdens of clinical trial participation, investments in telemedicine infrastructure will enable participants to sign consent forms online, receive medications in the mail or at local health care facilities, and undergo monitoring from afar. With support from the Cancer Moonshot, NCI is also funding research to enhance the engagement of patients in clinical trials and other research studies through technology and online networks.

> Telemedicine is a medical approach that uses technology to bring care to the patient, which eliminates the need for the patient to travel. Home-based participant interaction and monitoring will allow for more inclusive participation in clinical trials and better serve minority and underserved populations. Telemedicine may include remote clinic visits that occur via computer or phone, remote patient monitoring, or home-based care visits.

A survey conducted at Sidney Kimmel Cancer Center at Thomas Jefferson University revealed that 99% of adult patients with cancer who responded were satisfied with their telemedicine visits, and 87% of them felt telemedicine provided the same care as an in-person visit. In addition to learning from real world experiences, NCI has awarded grants to further study how telemedicine has impacted cancer care during the COVID-19 pandemic.

Telemedicine is only one way modern technology is being used to bring clinical trials to more people. With the widespread use of computers and smartphones, society has embraced digital technology in many aspects of life, including health care. Digital tools, such as health-related mobile apps, patient portals, wearable devices, and electronic health record, provide a rich source of information for clinical trials and open new avenues of access.

According to the latest Health Information National Trends Survey (2020), 85% of US adults use health or wellness apps, and 80% would be willing to share health data from a wearable device with their health care providers. Overcoming the logistical and data quality challenges of extracting clinical trial data from electronic health records and remote technology devices would greatly improve clinical trials.

In the first fully remote clinical trial led by the NCI Intramural Research Program, researchers will use a variety of digital tools to study the effects of a dietary and exercise intervention on health outcomes in melanoma patients being treated with immunotherapy. Participants will interact remotely with physicians, dieticians, and psychologists during telemedicine appointments. And with wearable technologies, fitness apps, and online databases, researchers will monitor how participants are adhering to their assigned interventions.

Part of NCI's efforts to incorporate telemedicine and digital technologies into clinical trials includes understanding telemedicine's limitations. Investments in digital research studies will address the ethical implications of remote clinical trials, issues of equal access to digital tools in underserved communities, challenges of making all electronic health records compatible between clinical trial sites, and study designs that create safe and secure ways for patients to contribute medical information to a health record.

Breaking Down Barriers to Clinical Trial Participation

Widespread patient participation in clinical trials improves the clinical trial process in many ways. Without it, the eventual research findings may not apply to all populations, and robust participation also improves the speed and efficiency of trials. Researchers are studying how to remove barriers to clinical trial participation, especially from underserved communities.

An NCI-funded study led by researchers at Fred Hutchinson Cancer Research Center examined why people with cancer do not participate in clinical trials. The researchers looked at trial availability, patient eligibility, and physical barriers. They found that more than three out of four patients could not enroll in a clinical trial because none were available in the area, or the patient was ineligible to enroll. This study suggests that limited enrollment is not due to patient unwillingness. NCI is working to address challenges to trial availability and eligibility.

Minority and underserved populations encounter additional barriers, including but not limited to distrust of clinical trials, lack of information about the process, time and resource constraints, and unawareness that trials exist.

Reaching Minority and Underserved Participants

To establish a treatment's safety and effectiveness in the general population, minority representation in clinical trials is critical. Yet, there is an imbalance in representation of minorities in clinical trials. For example, in the clinical trials that led to Food and Drug Administration approval of new drugs in 2020, only 8% of trial participants were Black or African American even though they represent 13% of the US population.

> Through programs like the NCI Community Oncology Research Program (NCORP), NCI supports community-based research by bringing clinical trials to patients within their own communities. Nearly a third of NCORP's community-based programs are designated as minority or underserved community sites.

NCI is actively working to reach, recruit, and retain clinical trial participants from minority and underserved populations. NCI-funded studies are making progress toward full representation, but there is room to improve.

Over the last two decades, the proportion of racial and ethnic minority patients enrolled in NCI-funded NCTN and NCORP clinical trials has nearly doubled—from 14% in 1999 to 25% in 2019. A large NCI-funded analysis found that 9% of trial participants in NCI's SWOG Cancer Research Network were Black, compared with less than 3% of participants in pharmaceutical company–sponsored trials. In the NCI Intramural Research Program, 13% of prostate and bladder cancer trial participants are Black, which is in line with the percentage of Black people with cancer in the US population.

Different populations of patients may also respond differently to therapies, and so clinical trials focused on those populations are important. For example, Black patients with cancer who are treated with some chemotherapies may have more neuropathy—weakness, numbness, or pain in the extremities caused by nerve damage. One ongoing NCI-funded study aims to reduce neuropathy side effects in Black women treated for breast cancer.

Increasing Eligibility and Reducing Cost

To reach all possible participants, including patients with coexisting health conditions, broadening eligibility criteria and reducing financial costs and other barriers to participation are critical factors.

In the last several years, NCI updated eligibility guidelines for NCI-sponsored cancer clinical trials. The changes aim to extend clinical trial access to more people, including those with coexisting health conditions. Many NCTN studies are now using more inclusive eligibility criteria.

With increased eligibility, clinical trials must ensure that participants are able to join the study without detriment to their families, employment, and finances. NCI has found that there is a lack of information about how clinical trial costs affect a patient's decision to join a study. Patient costs can include expenses to care for dependent family members; travel-related expenses to reach the clinical trial site; and, in the case of pediatric clinical trials, additional out-of-state medical costs for a guardian's own health conditions. More research is needed to understand how clinical trial study designs can ease financial burdens on patients.

COMPUTER-BASED DRUG DESIGN:
ADVANCING THE DISCOVERY OF NEW CANCER MEDICINES

Finding drugs to treat and prevent cancer is a difficult and expensive process. But, thanks to NCI-funded research, we have identified many biological targets for drugs based on a deeper understanding of how cancer develops and progresses. Decades of basic research combined with genome sequencing projects, such as The Cancer Genome Atlas, have revealed many genes that cause cancer and how they work in molecular pathways to either drive or suppress tumor growth. An increasing number of cancer drugs target these processes, thereby suppressing or killing cancer cells while minimizing the effects on normal cells. Research on the immune system and cancer is also leading to new therapies that engage the immune system in killing cancer cells.

Many innovative approaches are on the horizon, from drugs that specifically tag cancer cells for destruction to targeted signals that stop cancer cells from growing. While immense opportunities exist, drug discovery and development remain time consuming and costly. It can take 10 to 15 years for a new medicine to complete the journey from its initial discovery to its use in patients. These timelines do not necessarily include the many years of basic research discoveries that make clinical advances possible. Only 3%–5% of investigational cancer drugs that reach clinical trials receive Food and Drug Administration approval.

Typically, researchers find drugs by screening large numbers of small molecules for their ability to block the activity of a specific target that causes cancer. But even the largest collections of molecules—those with as many as one or two million compounds—represent a minuscule portion of all possible drug candidates. And testing these molecules is slow and expensive. Advances in computer-based drug design could greatly increase the odds of finding the best candidate drugs. Using computational methods, researchers can rapidly screen billions of molecules to find those that interact with targets in the body without having to physically make and test molecules in the lab. This sort of large-scale screening to find candidate drugs could dramatically speed drug discovery.

Computer-based drug design requires determining both the structure of a target molecule (such as an abnormal protein driving cancer cell growth) and the computational design of drug molecules that will bind to specific areas in that structure. Computational methods are already being used to fine-tune the shape of candidate drugs to help them attach more tightly and more selectively to their targets.

Improved computational techniques could identify the structure of key sites in targets where drugs can be most effective and predict how potential drugs may affect the behavior of the target molecules. In addition, improved computational methods could help predict the stability of candidate drugs in the body and, in the future, could be used to assess whether they may have unintended side effects.

Computer-based drug design will rely on the increasing availability of large amounts of information generated from laboratory research in biomedical sciences, without which computational techniques will not have enough data to return reliable results.

As computers get faster, and when quantum computing becomes available, the cancer research community is poised to make important leaps forward. Cancer is a particularly complex problem, but the field of cancer research has accumulated a great deal of knowledge about the mechanisms that drive cancer. Advances in computation could help greatly in identifying matches between targets in the body and prospective drugs.

Ending cancer as we know it includes a future where safe and effective medicines are available for every patient. Ultimately, having rapid computational methods, based on experimental data to predict interactions between potential drugs and targets in specific cancers, could open up a world of treatment and prevention options that work more effectively to save lives and cause fewer toxic side effects.

A Virtual Test Tube of Biological Structures and Medicines

One key challenge that computational techniques can help address is treatment side effects. Many molecules drop out of the drug development pipeline during clinical trials because of their toxic side effects. Avoiding side effects is especially important with drugs for cancer prevention that would be given to healthy people. With intensive computational modeling that builds on a rich trove of data, it will be possible to screen drug candidates for interactions with molecules in the body other than the intended target. For example, healthy cells and tissues may have slightly different versions of the same protein as drug targets. Computational modeling can help design drugs that match the target precisely enough to reduce the chance of side effects in such cases.

To enable this and other promising forms of computational modeling, more experimental data must be gathered in laboratory research and made publicly accessible. Proteins are the most important class of targets for cancer drugs, and researchers need clear pictures of many more proteins, including the same protein in different states. Support is needed to develop rapid, large-scale laboratory technologies to visualize the shapes of proteins in all their different configurations. The structures of some classes of proteins that are important cancer targets have been difficult to figure out using existing research techniques, and support is also needed to develop ways to solve their structures.

A developing technology called cryo-electron microscopy (cryo-EM) may help satisfy the need for more protein structures. Cryo-EM uses extremely low temperatures to capture the shapes of biological samples while they are suspended in water, very similar to the state in which they may exist in the human body. Higher-resolution techniques are leading to a boom in the number of protein structures that can be revealed by cryo-EM. Cryo-EM has the advantage of allowing researchers to solve protein structures quickly using samples that are not necessarily pure. Further research is needed to refine cryo-EM technology so that it can reveal structures with an even higher level of resolution that shows in detail the interactions between targets and potential drugs.

Over the last few years, cryo-EM has been used to reveal several protein structures that are important to understanding cancer, some of which are potential targets for drugs. For example, investigators in the NCI Intramural Research Program have used cryo-EM to get exceptionally high-resolution snapshots of a protein bound to an inhibitor and to obtain an image of a protein called p97 that is considered an attractive target for cancer drug development. NCI is making cryo-EM technology available to the research community through facilities at the Frederick National Laboratory for Cancer Research.

As computer-based drug design evolves, it can be used to screen not only small-molecule drug candidates, but also larger molecules, some of which mimic naturally occurring molecules in the body. Many such drug candidates take advantage of the body's immune response to target cancer cells.

One promising new category of cancer drugs that was developed with NCI support is called a proteolysis targeting chimera (PROTAC). These are two-headed molecules where one head attaches to a target protein, and the other head recruits an enzyme to degrade the protein to which the PROTAC attaches. This treatment

approach does not require designing a drug that can disable a protein by interfering with how it works, which can be complicated to achieve. It simply requires designing a drug that clings to the target protein long enough to label it for destruction, an interaction that may be easier for computers to model.

What the Government Can Do

While pharmaceutical companies ultimately bring most drugs to market, the federal government plays an important role in improving technology and developing the knowledge available to catalyze drug discovery and development. NCI can make critical data publicly available and get tools into the hands of researchers.

The federal government can make massive computational power available to analyze systems that are too complex for individual organizations to tackle on their own. For example, NCI has been working with the Department of Energy to make computational tools and data available to the research community. The government could potentially make virtual libraries containing billions of molecules available to the broad scientific community. NCI also establishes standards and quality control measures to ensure that its databases are uniformly of high quality. The government is well poised to ensure that aggregated data and computational resources are accessible to those who can use them to expand knowledge and develop drugs.

PRECISION PREVENTION: PREDICTING AND INTERCEPTING YOUR CANCER

Imagine if we were able to determine an individual's cancer risk by characterizing their genetic makeup, family history, environmental exposures, and behavioral factors and then tailor personalized prevention approaches based on these factors. To achieve this, we need a comprehensive biological understanding of the causes of cancer and cancer development to develop new interventions that reduce the risk of cancer. **This long-term goal—precision prevention—can end cancer as we know it by preventing suffering and death for those at risk and by helping those not at risk avoid unnecessary tests and treatments.**

Preventing the enormous burden of cancer means targeting its causes at every level—from promoting behaviors with widespread benefits, like eating a healthy diet and increasing physical activity, to developing precise molecular interventions that prevent premalignant conditions from becoming invasive cancer.

NCI-funded research has enabled prevention strategies that we already know work, including avoiding carcinogens like tobacco, vaccinating against cancer-causing viruses like human papillomavirus (HPV) and hepatitis B, treating H. pylori infections, and using screening and early detection to remove or destroy polyps, dysplasia, and other lesions. Some people at high risk use tamoxifen (Soltamox) and its derivatives to prevent breast cancers and aspirin to prevent colon cancers.

Further investments are needed to gain a deeper understanding of the causes of cancer and to develop additional strategies for targeted prevention interventions. One of the major challenges of cancer prevention is to avoid doing more harm than good, since most people are not at risk of developing life-threatening cancer any time soon and most abnormal cells will not progress to a lethal cancer. To prevent overdiagnosis and overtreatment, abnormal cells that will become aggressive need to be distinguished from those that will remain benign or nonlethal.

Ultimately, preventing cancer requires a multilayered approach. At the core, we need to understand not only the genetics of cancer cells and the biological changes that trigger runaway growth, but we also need to understand the microenvironment that allows tumors to grow in one person and thwarts their growth in another. We need to understand how a person's immune system, metabolism, and microbiome factor into tumor development and growth. Beyond tissues and the physical organism, we need to understand how people's behavior and environment affect their cancer risk, and what individual and environmental characteristics predict their ability

to adopt and sustain healthy behaviors. Approaches that integrate all of these variables are needed to fully realize the promise of cancer prevention.

With greater investment, NCI will be able to catalyze new discoveries into the biological causes of cancer and support the development of tools and technologies to move personalized prevention strategies forward for all people.

Understanding Which Cells Become Cancer and How to Target Them

Achieving precision prevention requires a more complete understanding of how specific cancers develop. Due to NCI's long-term investments, researchers now know many of the genes that can cause cells to divide without restraint. Some cancer-causing genetic changes are inherited, but most are not. The same mutations that one person inherits can also arise through infection, exposure to carcinogens, or random chance.

But the link between genetics and cancer is not necessarily straightforward. Many healthy people carry cancer driver mutations but they do not have any sign of cancer. Researchers have come to understand that cancer results from a dynamic interaction between genetic changes in cells and individual susceptibility. Researchers are looking into what keeps cells that carry driver mutations from progressing to cancer as well as the factors that lead to cancer development and progression, including the roles of the tissue microenvironment and immune system. Learn more about NCI's strategy to develop tumor atlases to predict cancer development and progression.

Ongoing research to understand the early stages of cancer development and the biological mechanisms that protect against cancer can pay off in the form of better prevention and screening approaches. For example, researchers at Boston University and their collaborators showed that it is possible to stratify premalignant lesions in the bronchi of people undergoing lung cancer screening according to the likelihood that the lesions will progress to lung cancer. The researchers identified four distinct subtypes of premalignant lesions based on their molecular features and immune interactions. Their findings also suggested strategies that use the immune system to prevent the more dangerous lesions from progressing to lung cancer.

Leveraging the power of the immune system to prevent cancer is an active area of research. Immense opportunities exist because of decades of NCI investments in understanding the interactions between cancer and the immune system.

Cancer immunoprevention—engaging the immune system to help prevent cancer—for individuals with Lynch syndrome is just one example. People with the syndrome have up to an 80% lifetime risk of developing colorectal cancer and several other types of cancer. Lynch syndrome is an inherited predisposition to cancer caused by mutations in a small number of genes involved in DNA repair. These mutations lead to the production of unusual protein fragments that are not present in normal cells. Researchers had the insight to treat these protein fragments as targets for a vaccine that trains the immune system to kill cells if they express those protein fragments.

Mice with the equivalent of Lynch syndrome that have received such a vaccine develop fewer cancers and survive longer, especially when they also receive an anti-inflammatory NSAID medication. A study in people with Lynch syndrome who have a history of cancer showed that this vaccine approach is safe, and additional clinical studies are planned to test the vaccine's effectiveness in preventing cancer.

The most important risk factor for cancer is age, but the reasons why that's true are not clear. Some researchers believe that age simply reflects more time for tumors to develop, but older people also undergo physiological changes, such as in the immune system, that we do not fully understand. For example, even though aspirin has been shown to prevent cancer in some cases, a clinical trial funded by NCI and others found that taking low-dose aspirin daily may actually increase the risk for cancer in those over age 65. Aspirin is known to influence molecular processes relating to the initiation, progression, and spread of cancer. Understanding why age makes a difference in this context—and in other contexts—will help improve prevention approaches across the lifespan.

Improving Cancer Prevention through the Promise of Technology

Cancer researchers are confident that precision prevention will become a reality through a deep biological understanding of cancer development coupled with new tools and technologies. These technologies include powerful computational methods, wearable data collection tools, sophisticated but practical screening and diagnostic platforms, and advanced research tools such as human organs on chips.

Better computational tools are needed both to move research forward and to develop more effective interventions. Cancer is incredibly complex, so investments in large-scale computational approaches are needed to integrate data about the biological causes of cancer and to stratify cancer risk. Improvements in technologies that make collecting data less costly and less burdensome, like wearable sensors and telemedicine tools, may help researchers engage larger numbers of people to gather data for research and to deliver interventions.

NCI is supporting numerous lines of research to further incorporate a molecular understanding of cancer into cancer screening. For example, NCI-funded researchers are figuring out how to integrate imaging technologies with biomarker testing to help distinguish lesions that may be life-threatening from those that are not. This type of screening is important to avoid the physical, psychological, and financial costs of overdiagnosing and overtreating lesions that will not be harmful to the patient.

> Cancer screening tests can find cancer at early stages, and some tests can also help to prevent cancer by detecting premalignant lesions that can be removed or destroyed before they become cancerous. Current screening tests typically detect one type of cancer or precancer at a time. In the future, early detection and screening approaches using liquid biopsies may detect multiple cancers simultaneously.

A rapidly evolving technology for the early detection of cancer is the liquid biopsy test, which typically relies on a simple blood draw. Researchers are developing tests to detect cancer-related molecules secreted in the blood to screen for multiple types of cancer at once. Highly sensitive and specific tests are needed for this purpose, to reliably detect low levels of circulating DNA or proteins while minimizing the chances that a test incorrectly indicates the presence of cancer.

NCI-funded investigators at Johns Hopkins University recently reported on a multicancer blood test that detected early stages of cancer in women with no prior history of cancer, including cancer types for which no screening tests currently exist. The researchers suggest such screening could become routine to detect cancers earlier and treat them before they become life-threatening. In the study, the screening test led to few unnecessary follow-up tests. With additional support from NCI's Small Business Innovation Research (SBIR) Program, PapGene, acquired by Thrive Earlier Detection Corp. of Cambridge, Massachusetts, is further developing this technology. More research is needed to assess the balance of risks and benefits of such screening, its cost-effectiveness, and whether the approach improves long-term outcomes for patients.

While liquid biopsy tests are still being developed for early detection, such tests are already used in the clinic to help diagnose cancer, to guide treatment decisions, and to monitor for cancer recurrence. In the future, liquid biopsy tests could be used to detect early changes in the disease development process in order to intervene and prevent invasive cancer.

While early detection is not as desirable as preventing cancer from developing in the first place, tests that detect early stages of cancer are improving quickly and are poised to help people by detecting tumors before they become life-threatening. In addition to detecting early stages of cancer, liquid biopsies could potentially detect biomarkers that indicate a risk for cancer before the disease arises. These screening tests will have to be evaluated to assess whether they truly help improve patient outcomes. NCI is well-suited to evaluate the benefits and harms of such tests.

TUMOR DYNAMICS: PREDICTING CANCER'S TRAJECTORY USING TUMOR ATLASES
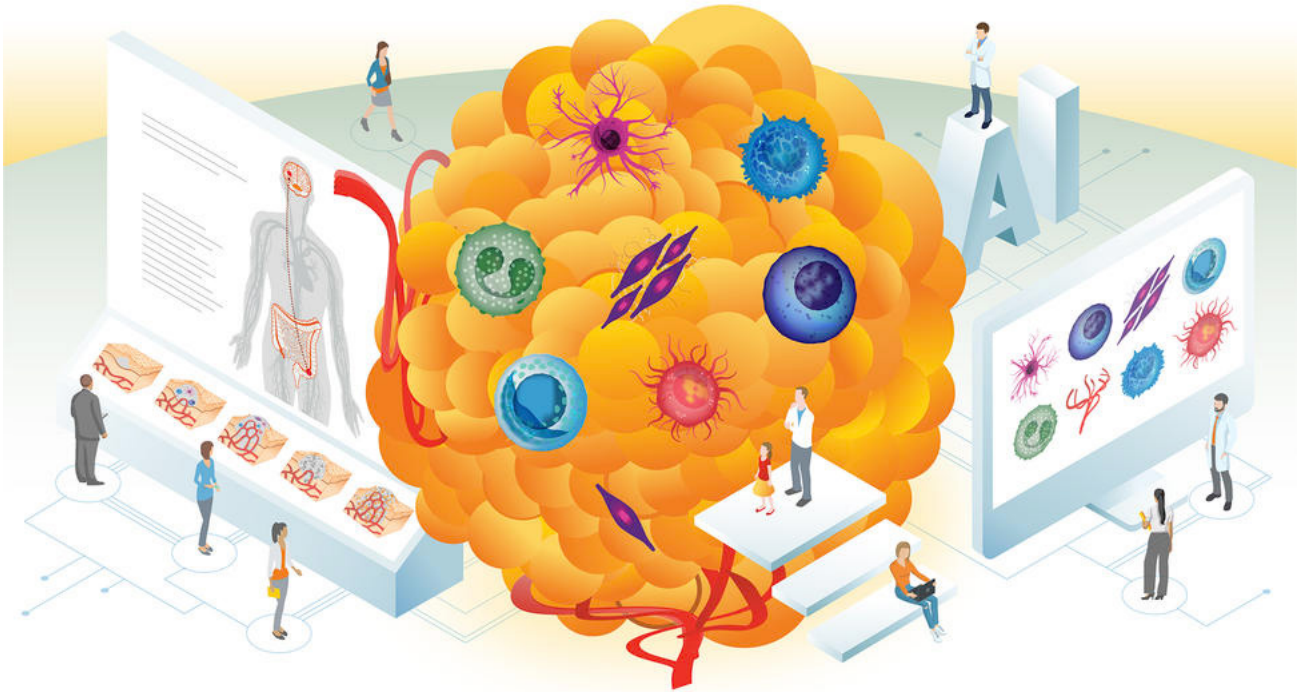
Cancer is a dynamic disease that is unique to each patient. Tumor development and progression are complex, involving factors in the cancer cells themselves as well as multidimensional interactions between other cells and tissues in the body, which are shaped by a person's genetics and cumulative exposures. As cancer progresses, tumors typically become more heterogeneous, composed of diverse cancer and noncancer cells with different molecular characteristics and behaviors. This staggering complexity makes it difficult to predict how a person's cancer will progress and respond to treatment.

NCI is addressing this challenge by supporting research that is accelerating our understanding of the dynamics of tumor progression. For example, as part of the Cancer Moonshot, scientists are creating 3-D reconstructions of tumors and their evolution through the Human Tumor Atlas Network (HTAN), which consists of 10 interdisciplinary research centers across the country. HTAN brings together information about the cellular and structural makeup of a variety of adult and pediatric tumor types and premalignant abnormalities down to the single-cell and molecular level. In addition, NCI supports research to build and test new computational approaches to predict cancer development, progression, and response to treatment.

Technological advances, such as genetic sequencing of tumors at the single-cell level and spatial analysis of gene expression patterns across cells within a tumor sample, are enabling scientists to study tumors at unprecedented resolution. With these advances, researchers are exploring each tumor's set of genetic and molecular characteristics, including in the cells and molecules surrounding cancer cells, to create maps of a tumor and its microenvironment.

While each tumor is unique, scientists can begin to understand which genetic and molecular characteristics are linked to tumor behavior by comparing tumor data maps to each other and to patient outcomes. However, this requires processing and interpreting a lot of data. New mathematical approaches and computer programs— including artificial intelligence (AI) and deep learning—can be used to analyze tumor data and enable researchers to better define key transitions during cancer progression, such as premalignancy to cancer and primary cancer to metastasis.

Ending cancer as we know it includes a future where we can predict a tumor's trajectory based on a detailed profile of each patient's disease. Additional research investments coupling tumor atlases with advances in computer science and molecular techniques will ultimately enable precision prevention, treatment, and care strategies for patients.

Using Computer Science and Artificial Intelligence to Study Tumor Progression

Recent advances in data access, computing power, and AI methods are enabling a better understanding of tumor progression, from premalignancy to early cancer and from less to more aggressive cancer.

AI is no longer just fodder for science fiction stories. Instead, cancer scientists are using AI and machine learning to make sense of the large amounts of data being generated on the dynamics of tumor evolution. As noted above, these types of data include detailed molecular characteristics and physical features of single cancer cells, tumor images and other spatial data, and clinical information over the course of diagnosis and treatment.

> **Artificial intelligence (AI)** is a computer's ability to perform a task in a way similar to that of humans, through a process of learning, reasoning, and acting based on computer program instructions. **Machine learning** and its subset **deep learning** are types of AI that learn by exploiting patterns in data.

As one example, an NCI-funded collaboration between researchers at Indiana University and the NCI Intramural Research Program applied innovative and faster AI techniques to reconstruct key features of tumor progression, a computational process that can be prohibitively slow. The researchers used deep learning methods to understand the evolutionary history of a tumor using measurements from single cells. Notably, the researchers were able to construct large "family trees" of tumor cells to infer the history of how tumors evolve over time. In the future, this approach should enable scientists to better understand how cancer forms, progresses, metastasizes, and responds to treatment, which can lead to new therapeutic targets and approaches.

There are still major hurdles to address before AI will reach its full potential in cancer research. One major hurdle, called the "black box" problem, is AI's lack of transparency. We don't fully understand how the computer uses patterns in the data to make decisions. With additional investments in AI design and implementation, researchers hope to establish transparent and reliable computer programs that can use tumor data input to help predict clinical outcomes for patients when making treatment decisions.

Compiling Data on Tumor Heterogeneity with Cutting-Edge Technology

Large data sets that represent the cellular and molecular diversity of tumor cells are the ingredients for AI tumor analysis. Tumors consist of cancer cells as well as immune cells, blood vessels, fibroblasts, other cells, and components that interact with the cancer cells.

The molecular characteristics of cells in a tumor differ from patient to patient and even among tumors in a single patient. And these characteristics can change over time, including in response to cancer treatments. Understanding tumor cell heterogeneity, and collecting data that capture this heterogeneity, is critical because the extent of molecular differences among tumor cells might affect whether it grows or not (its stability), its ability to evade the immune system, whether and where it spreads (metastasizes), and its susceptibility to treatments.

The heterogenous mixture of cells in a tumor has multiple molecular and physical features that scientists can observe. Collecting and analyzing this combination of data that describes cells is called multi-omics.

Multi-omics, the process of collecting and analyzing a combination of data that describes cells, provides a way to study tumor cell heterogeneity, and can be performed at even the single-cell level. Some types of data that scientists collect include:

- genomics (DNA sequences in the cell)

- epigenomics (DNA modifications that affect whether a gene is turned on or off)

- transcriptomics (RNA sequences that cells use to make proteins)

- proteomics (the set of proteins in a cell)

- metabolomics (the products of cells breaking down proteins and nutrients)

Single-cell sequencing is a rapidly growing technique that allows scientists to compare the genomes and DNA products from each tumor cell. This effort builds on previous NCI-funded cancer genomic studies that relied on sequencing a whole tumor sample containing multiple cell types at a single point in time. Using single-cell technology, a recent NCI-funded study led by investigators at Memorial Sloan Kettering Cancer Center identified a subpopulation of small cell lung cancer cells—with unique genetic features and an immunosuppressed microenvironment—that is more likely to metastasize to other parts of the body. These findings have implications for developing future targeted immunotherapies for small cell lung cancer.

In the next frontier of cancer research, scientists are leveraging cutting-edge technologies to learn about the spatial anatomy of cancer and its molecular features. One such imaging technique uses repeated fluorescent labeling to identify a large set of cellular markers throughout a single biopsy. Imagine cutting a tumor into small sections and then using multiplex imaging to record many cellular and molecular features of each section at the single-cell level. Scientists are doing just that, and then assembling that information virtually to build a 3-D map of the tumor and its microenvironment. By mapping out heterogeneous tumor cells and their microenvironments, scientists are poised to identify cellular interactions and molecular characteristics that predict tumor behavior.

For example, NCI-funded researchers at Stanford University used spatial proteomics to characterize HER2-positive breast cancer collected before, during, and after treatment with neoadjuvant (presurgical) therapy. Typical tumor samples are an aggregate of tumor, immune, and connective or structural cells. By using spatial proteomics, they found that the number and kind of immune cells in the tumor changed during treatment for a subset of patients, and that increased levels of a single immune marker, called CD45, following initial treatment could predict response to the full course of therapy.

These results add to the groundwork for personalized medicine. Imagine tailoring a patient's treatment plan based on their tumor's molecular response to initial therapy, increasing the likelihood that treatment will lead to a favorable outcome.

In another study, NCI-funded researchers at the Oregon Health & Science University generated a comprehensive multi-omic analysis of a human cancer response to treatment. They analyzed blood and tumor biopsies from a patient with metastatic hormone receptor–positive breast cancer during multiple rounds of treatment. Samples included the primary tumor and three subsequent metastatic tumors over the course of 42 months. The researchers used the data to generate a spatial image atlas to identify how the patient's tumors responded to treatment and to identify patterns of tumor progression and mechanisms of drug resistance.

These studies offer a peek into the possibilities for precision medicine in the future, in which multi-omics data will help doctors optimize treatment decisions for their patients. More investments are needed to develop the next generation of technology to perform spatial analysis dynamically, at a larger scale, and more rapidly.

Studying the Role of the Tumor Microenvironment

Just as plants and animals respond to the demands of their environments, tumors also adapt to environmental pressures. Cancer scientists are increasingly thinking about tumors from an evolutionary and ecological perspective. New research aims to reveal how a tumor's microenvironment affects tumor growth, metastasis, and drug resistance.

> The **tumor microenvironment** is made up of the cells and molecules that surround the tumor. For example, blood vessels feed the tumor and immune cells may prevent the tumor from growing or spreading.

Immune system function is an important factor in the tumor microenvironment. The immune system patrols the body to watch out for abnormal cells and can recognize and kill cancer cells—a capacity that has been harnessed by cancer immunotherapies. Scientists want to better understand how tumor cells interact with cells of the immune system so they can develop more effective immunotherapy and immunoprevention approaches. For example, researchers want to learn how and when precancerous tumors that progress to cancer, or cancerous tumors that recur after therapy, hide from the immune system.

In an NCI-funded clinical trial testing different drugs for early-stage HER2-positive breast cancer, doctors collected information about the tumor's immune microenvironment with each therapy. They found significant changes in the composition of surrounding immune cells 14 to 21 days after treatment. They found that an initial increase in cancer-killing T cells decreased by the time of surgery. In the future, this type of information could help determine the best timing for immune system–based interventions during breast cancer therapy.

Now, tumor atlases are being compiled to study the tumor microenvironment's role in the transition from premalignancy to invasive cancer—with an eventual goal to incorporate patient exposure data over time. This information could inform prevention and intervention strategies in the future.

For example, NCI-supported researchers at Stanford University and their collaborators observed a correlation between the tumor microenvironment and breast cancer development. Using surgical samples from patients, their study revealed that changes in the location and function of immune cells surrounding the tumor are associated with a shift from preinvasive abnormalities to invasive breast cancer.

Building on NCI-funded research on the tumor microenvironment, scientists have suggested tumor classification systems that may help doctors select the best course of treatment for individual tumors. These classifications are often based on the genetic makeup of the tumor. However, researchers have developed a classification system that is based on evolutionary and ecological principles, incorporating inherent traits of the tumor (such as tumor cell heterogeneity and rate of tumor change) and the ecology of the tumor's surroundings (such as blood flow and immune system response). A classification system that includes tumor and tumor microenvironment traits could aid the goal of precision medicine.

PARTICIPATING IN A COLON CANCER TRIAL USING TELEMEDICINE

While COVID-19 surged in the United States in 2020, a colonoscopy revealed that Marilyn had stage III colon cancer. "I had no symptoms of colon cancer, so I was surprised to hear I had it," Marilyn said. She's glad she listened to her doctor and had the cancer screening test.

Facing cancer can be daunting, but Marilyn had been up to the challenge twice. She had been treated in the previous 5 years for kidney and breast cancers, and both were in remission. Her colon cancer diagnosis and treatment, however, came with new challenges: required social distancing and safety practices because of the COVID-19 pandemic. As much as possible, she and her clinical care team adapted to telemedicine practices, engaging via telephone and video instead of in-person visits. And Marilyn has appreciated the ease of staying in contact with them.

"At times, I've had to talk with my doctor on the phone. He would call me, and we would talk. I felt supported," she recalled. "All my doctors are looking after me."

When her cancer doctor suggested she enroll in an NCI-sponsored phase 3 clinical trial offered locally through Marshfield Medical Center, an affiliate of the Wisconsin NCI Community Oncology Research Program community site, Marilyn readily agreed. The trial is testing the effectiveness of adding the immunotherapy agent atezolizumab (Tecentriq) to standard combination chemotherapy given after surgery to patients whose colon cancer has a molecular feature called mismatch repair deficiency.

Marilyn is participating in an NCI clinical trial using telemedicine practices.

Credit: Photo courtesy of Marilyn

"If it may help me and help somebody else, let's do it," she said. She underwent surgery to remove the tumor and 12 inches of her lower intestine, and continues to receive treatment through the ongoing clinical trial.

Marilyn is looking forward to visiting her sister in Oklahoma and spending time with her 14 grandchildren and 8 great grandchildren. She'll continue to share her cancer experiences with her family and friends. "I told my grandkids that anytime you feel like something's not right, don't be afraid," Marilyn said. "It doesn't hurt to call the doctor and ask them. That's what they're there for."

INHERITED RISK FOR PROSTATE CANCER SPURS RESEARCH PARTICIPATION

A preponderance of cancers among family members fueled Joe's concern that he may have a genetic predisposition for cancer. He decided to have genetic testing in 2003, and the testing showed that he carried a *BRCA2* mutation.

While *BRCA* mutations are best known for their association with an increased risk of breast and ovarian cancers in women, alterations in BRCA genes can also increase a man's risk for prostate cancer. Men who have inherited alterations in *BRCA* and other genes are much more likely to be diagnosed at a younger age and have prostate cancer that is aggressive. This knowledge spurred Joe to schedule annual appointments with doctors, consult a geneticist, and join social networks.

While participating in an online group for men with *BRCA* mutations in early 2019, Joe heard about an NCI study to develop better ways of detecting prostate cancer early in high-risk populations. Men with *BRCA* and other high-risk genetic alterations who enroll are screened for prostate cancer using multiparametric magnetic resonance imaging (mpMRI).

It is current practice to use a PSA test to aid prostate cancer screening. Yet, the correlation between PSA level and a prostate cancer diagnosis in men with *BRCA2* or other mutations is unknown; there is no standard way to screen men with high-risk genetics for prostate cancer. While MRI scans produce detailed images of organs and tissues in the body, mpMRI technology provides more precise scans that can help doctors find and

Thanks to an NCI research study, Joe's prostate cancer was found at an early stage.

Credit: Photo courtesy of Joe

biopsy prostate tumors far better than a standard MRI. The goal of the NCI study is to develop better ways of detecting prostate cancer early in high-risk populations. The researchers also plan to follow enrollees over the years to learn more about the natural history and progression of prostate cancer.

Joe enrolled in the study in spring 2019 and went to the National Institutes of Health (NIH) Clinical Center to meet the NCI clinical care team, undergo laboratory tests, and have an mpMRI scan. On the way to the airport to fly home to California, he received a call from the NCI clinical care team asking him to come back to the NIH Clinical Center. They saw something on his mpMRI scan.

Joe returned to NIH, learned he had a tumor, and agreed to have a biopsy. "I was blown away by the accuracy of the biopsy technique that NCI used," he recalled. "Cancer can be anywhere in the prostate and can be missed by a typical biopsy, which involves sampling multiple random areas. But in my case, we had the mpMRI scan. We knew where my small tumor was located."

Using the highly detailed scan, Joe's doctors were able to pinpoint the exact location of the tumor and sample tissue from that area. Examination of the specimen revealed cancer.

Several months later, Joe elected to have his prostate gland surgically removed in California. The pathology revealed an aggressive prostate cancer confined to the gland. While Joe no longer comes to the NIH Clinical Center for mpMRI screening, he continues to follow up with his NCI care team by phone.

In 2021, Joe is back to training for a 500-mile, week-long cycling event to raise funds for people with arthritis. This was an activity he put on hold for 2 years due to his prostate cancer experience and the COVID-19 pandemic. And NCI continues to enroll men with BRCA2 mutations in the mpMRI study.

The 1960s saw a surge in activism to end widespread institutionalized racism, including in health care, where little was being done to study and address disparities. Since then, progress has been made in areas like inclusive cancer data collection, community outreach, and organizational change within medical institutions. But as is evident from current social justice movements and the COVID-19 pandemic, disparities still exist and remind us how much is left to do to build a truly equitable society.

NCI Equity and Inclusion Program

Learn how NCI will help end structural racism in biomedical research and why the program was launched.

Don't Just Talk to Patients, Listen to Them!

"I know what it feels like to appear healthy and have health problems dismissed," said breast health disparities researcher and cancer survivor Dr. Vanessa Sheppard. "We need to inform patients but also listen and trust that they know their bodies."

Vanessa was diagnosed with Hodgkin lymphoma in college and battled it three more times. Throughout, she felt that "there was information I didn't have access to." Even years later, she was surprised to see Hodgkin lymphoma listed on a colleague's slide as a risk factor for breast cancer. "I'm fairly educated, and my risk was not clear to me." As a result of the radiation treatments in her youth, Vanessa would go on to be diagnosed with (and overcome) triple-negative breast cancer.

Vanessa's deep commitment to making people feel heard is what drives her work as associate director of community outreach at VCU Massey Cancer Center. "As researchers, we can enhance our relationships in underserved communities if we embed community voices in what we do and participate in a dialogue," she said. She added that having that dialogue with the Latina, African immigrant, and African-American women that the center sees could help increase breast cancer screenings and clinical trial participation in these communities. Through initiatives like partnering with a cohort of community champions, Vanessa is dispelling myths about breast cancer and clinical trial participation.

This year, she got to tell her story and discuss her work with Dr. Jill Biden during the First Lady's visit to VCU Massey. "In that moment, I thought of the people close to me who didn't have good outcomes," she said. "I stand on the shoulders of those before me. I'm here, and I can pay it forward to other minority and underserved individuals."

Dr. Vanessa Sheppard told her own story of survivorship and discussed community outreach and engagement efforts with Dr. Jill Biden during the first lady's visit to VCU Massey Cancer Center in February 2021.

Credit: Official White House Photo by Ana Isabel Martinez Chamorro.

A CANCER RESEARCH CAREER SPARKED BY A DIAGNOSIS OF HER OWN

AnnaLynn Williams, Ph.D., was a 22-year-old graduate student pursuing a career in clinical research when she was diagnosed with acute myeloid leukemia (AML). She underwent treatment for 3 years, including a bone marrow transplant. After reading the consent form before the transplant, she had more questions than her doctor could answer. "The idea that the very treatments that were saving my life were likely going to cause a whole host of issues later on in life—that hadn't occurred to me," she recalled. "I started to dig deeper, and that's where I found my passion."

With her cancer in remission, AnnaLynn returned to the University of Rochester School of Medicine and Dentistry, inspired to focus her research on oncology. While pursuing her master's degree and Ph.D. in cancer epidemiology and encouraged by a mentor, she applied for several NCI career development awards. She was thrilled to receive the NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00), which supports outstanding Ph.D. and other research doctoral candidates. "Having this training award allowed me to focus on the science I wanted to focus on and gain experience and training in cancer control research," she noted. "Going into the postdoctoral stage with the award provided me a lot of autonomy that most postdoctoral investigators don't have."

After her cancer diagnosis, Dr. AnnaLynn Williams focused her career on cancer research with the support of several NCI early-career development awards.

Credit: Photo courtesy of AnnaLynn Williams, Ph.D.

As AnnaLynn was moving to a postdoctoral position at St. Jude Children's Research Hospital, her program officer at NCI encouraged her to consider the NIH Pathway to Independence Award (K99/R00), which provides mentored training and helps early-career investigators develop the skills to establish a strong, independent research program. She used her initial F99/K00 award to take a short course in epigenetics that better prepared her to write a successful K99/R00 grant application.

AnnaLynn's K99/R00 award focuses on the early and late effects of Hodgkin lymphoma and its treatment in adolescent and young adult survivors, including accelerated aging processes that may lead to neurocognitive impairment. "The cancer treatments we've given young people have sent them on a unique biological aging trajectory. We shifted them off the path they would have been on if they'd never had cancer," AnnaLynn explained. "We think some of that early biological and physiological aging that we see in this population group is also contributing to premature cognitive aging." Her grant focuses on associations between age-related biomarkers and neurocognitive function.

AnnaLynn's commitment to help survivors of adolescent and young adult cancers remains strong, and she is grateful for the opportunities provided by the NCI career development awards she received. "I got into survivorship research because I myself am a survivor. I just want to help cancer patients and survivors not only make it through treatment but live healthy and full lives afterward."

A FAMILY'S EXPERIENCE INSPIRES A CAREER IN PANCREATIC CANCER RESEARCH

Florencia McAllister, M.D., has dedicated her career and her research to pancreatic cancer since watching her mother succumb to the disease. "The pathologist showed me her tumor. It was just the tiniest tumor," she said. "It was unbelievable that just a few months afterward she would have a liver full of metastases." Pancreatic cancer often spreads to the liver. As a doctor, this experience made Florencia more empathetic to what people with cancer and their families go through. It also drove her as a researcher.

Her path to becoming a physician–scientist started in Argentina when, at age 15, she set her sights on a medical degree. A 1-month training opportunity at a US university hospital after finishing medical school piqued her interest in research. Florencia then joined a laboratory in New Orleans and began studying how gene therapy can modulate the immune system to fight infections.

When that laboratory moved to Pennsylvania, Florencia relocated with it and learned how to set up a new lab. "I learned research by doing it, through hands-on experience," she reflected on her career journey. She completed her medical residency while conducting research. It was during this time that Florencia lost her mother, and she pivoted her research focus to cancer.

She pursued fellowships in oncology and clinical pharmacology and gained further expertise in cancer genetics, mouse models, and tumor immunology until she accepted her current tenure-track position at the University of Texas MD Anderson Cancer Center. Her research remains centered around pancreatic cancer, which is often diagnosed at a late stage, lacks effective treatments, and has a high death rate.

With support from NCI, Dr. Florencia McAllister is pursuing new ways to prevent and treat pancreatic cancer.

Credit: Photo courtesy of Florencia McAllister, M.D.

Using mouse models, she found that immune cells that secrete a particular protein, IL-17, promote the growth of pancreatic tumors. And some bacteria in the gut may be partly responsible for triggering a response by the immune cells that secrete IL-17 and so increase IL-17 levels in the body. To further study how gut bacteria may trigger immune responses, and to develop interventions to treat pancreatic cancer with the long-term goal of preventing it, Florencia applied for and received an NCI individual investigator award (R01) and was happy to learn that NCI had converted her grant to a MERIT Award (R37).

The R37 award provides the possibility of 2 additional years of funding, for a total of 7 years of support. "It's fantastic for anyone who is starting their research career," Florencia stated. "To have that extra time is super helpful. It gives me security so that I can, for a good amount of time, continue pursuing my cancer research rather than spend a lot of time applying for a lot of grants." Florencia intends to spend that time pursuing better ways to treat pancreatic cancer in her mother's memory.

DEVELOPING A UNIQUE RESOURCE TO OVERCOME CANCER DISPARITIES IN AFRICAN AMERICANS

When Clayton Yates, Ph.D., was 15 years old, he lost his grandfather to prostate cancer. "He was my baseball buddy. I played, and he came to my games," Clayton recalled. "After his death, I was determined to figure something out about prostate cancer. I had to stop it."

While getting his bachelor's and master's degrees at Tuskegee University, Clayton worked in a laboratory studying prostate cancer, where the principal investigator encouraged him to become a scientist. Clayton left his home state of Alabama to earn his Ph.D. and complete his postdoctoral training. Yet, the experiences of his formative years drew him back to Alabama. He returned to Tuskegee as an assistant professor, where he has been supported through NCI's Partnerships to Advance Cancer Health Equity (PACHE) program.

With support from NCI, Dr. Clayton Yates developed a cell line now used to study prostate cancer in African-American men.

Credit: Photo courtesy of Clayton Yates, Ph.D.

PACHE supports partnerships between institutions serving underserved health disparity–populations and students underrepresented in biomedical research and NCI-Designated Cancer Centers. Tuskegee's PACHE partnership award is jointly shared with the O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham and the Morehouse School of Medicine in Atlanta.

Clayton's research efforts focused on developing cell lines from African-American men with prostate cancer to determine if there are molecular or genetic differences that contribute to aggressive prostate cancer in African Americans. These cell lines are now among the most widely used to study prostate cancer in this population. To further advance cancer disparities research, Clayton has also developed cell lines for breast, pancreatic, and colorectal cancers in African Americans.

Clayton and his colleagues are continuing their research on prostate cancer. One activity involves a clinical trial to test therapies based on Clayton's discovery of a biomarker called Kaiso, which has been found to predict cancer aggressiveness in African Americans. In addition, using supplemental funding to the PACHE award, Clayton is working with Nigerian scientists to dissect the role of ancestry and the impact of the trans-Atlantic slave trade on the disparities seen in African-American men with prostate cancer.

"I can't imagine where my career would be without NCI support," Clayton said. "For each milestone I achieved, NCI funded it in whole or with other funders. NCI has been there every step along the way, supporting the vision to address and solve cancer disparities and achieve health equity."