SPOTLIGHT ON **Immunotherapy**

AACR CANCER PROGRESS REPORT 2023

ADVANCING THE FRONTIERS OF CANCER SCIENCE AND MEDICINE

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ABOUT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 54,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 130 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting. In addition, the AACR publishes 10 prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit **AACR.org**.

A Message from AACR

We are in an era of extraordinary scientific progress against cancer. In the United States, overall cancer death rates are continuing to decline, and the number of cancer survivors has reached a record high. Breakthroughs across the spectrum of cancer science and medicine are contributing to unparalleled advances against previously intractable diseases, such as advanced lung cancer and metastatic melanoma. Thanks to the new wave of scientific discoveries and technological innovation, we are now poised to deliver transformative advances that will save even more lives from cancer.

The *AACR Cancer Progress Report 2023* provides a comprehensive overview of the remarkable progress we are making because of medical research, much of which is supported by federal investments in the National Institutes of Health (NIH) and the National Cancer Institute (NCI). As highlighted in the report, federal funding for medical research has enhanced our understanding of the complexities of cancer and accelerated the rate at which this knowledge is being harnessed to develop new and better approaches to preventing, detecting, diagnosing, treating, and curing cancer.

Among the advances detailed in the report are the 14 new anticancer therapeutics that were approved by the U.S. Food and Drug Administration (FDA) between August 1, 2022, and July 31, 2023.

Among the new treatments is the first antibody-drug conjugate, a type of molecularly targeted therapeutic, approved for treating patients with ovarian cancer harboring a specific biomarker. Another major advance in cancer medicine is the FDA approval of a molecularly targeted therapeutic specifically directed against the altered protein arising from a mutated *KRAS* gene, one of the most commonly mutated genes in human cancers. This remarkable achievement—the drug being only the second of its kind to receive FDA approval—was made possible by decades of laboratory and clinical research. As we continue to discover the molecular and cellular underpinnings of the collection of diseases we call cancer, there will be more groundbreaking discoveries that further advance the frontiers of precision cancer medicine.

As showcased in the report, decades of basic research in the field of immunology have led to a surge in the impact of cancer immunotherapy, the newest pillar of cancer treatment that has revolutionized patient care. The use of immune checkpoint inhibitors (ICI), which are immunotherapeutics that work by releasing brakes on the natural cancer-killing power of the immune system, has expanded at an unprecedented pace over the past decade. In January 2013, there was only one FDA-approved ICI for treating just one cancer type. As of July 31, 2023, there were 11 ICIs approved by FDA, and at least one ICI has been approved for treating 20 different types of cancer and any type of solid tumor characterized by the presence of specific molecular signatures, or biomarkers.

CAR T-cell-based immunotherapies, which are currently approved for an array of hematologic cancers, have ushered in a new era of personalized medicine because they are generated by the genetic engineering of a patient's own immune cells to attack his or her cancer cells. Expanding our knowledge about the immune system and how it interacts with cancer cells, and facilitating the convergence of experts from an increasingly diverse array of disciplines, will create even more opportunities for pioneering advances in immunotherapy for the benefit of patients around the world.

Despite these significant strides against the disease, we must continue our quest for newer and more innovative methods to prevent and cure cancer while improving the quality of life of our patients. This urgent need is underscored by the sobering reality that nearly 2 million American will be diagnosed with cancer in 2023. This number is predicted to increase considerably in the coming decades because cancer is largely a disease of aging, and the segment of the U.S. population age 65 and older is growing. Therefore, it is critical to implement newer and more effective strategies for cancer prevention, early detection, diagnosis, and treatment.

Moving forward, we must also ensure that everyone benefits from the groundbreaking advances against cancer. As highlighted in this report, racial and ethnic minorities and other medically underserved populations shoulder a disproportionate burden of cancer. Participation of patients from these population groups in clinical trials that are testing lifesaving new anticancer therapeutics continues to be disappointingly low. We must adopt new approaches to inform, educate, and encourage cancer patients to enroll in clinical trials so that researchers can identify the most efficacious approaches to help all patients. As a scientific organization whose core values include diversity, equity, and inclusion, AACR is fiercely committed to addressing all inequities in cancer research and patient care and to ensuring sociodemographic diversity in the cancer workforce so that it is reflective of the patient population it serves.

Looking to the future, we strongly believe that we have never been in a better position to take lifesaving cancer science

from the bench to the clinic. Thanks to bipartisan leadership in Congress that has delivered steady and significant annual funding increases for NIH and NCI, we now have the scientific knowledge, cutting-edge technologies, and capability to deliver unprecedented advances to all cancer patients. As the first and largest professional organization in the world dedicated to advancing all areas of cancer science and medicine, AACR is thrilled to work alongside the administration and complement the NCI's National Cancer Plan to meet the goal of the reignited Cancer Moonshot of reducing the cancer death rate by at least half by 2047. To address the nation's cancer mission and its challenges at the earliest possible time, AACR launched the AACR Cancer Centers Alliance on September 13, 2023. This formal partnership with the nation's cancer centers will serve as a catalyst to marshal their resources and collaborate directly, effectively, and synergistically to propel new lifesaving cures for the millions of people whose lives are touched by cancer.

To maintain the momentum against cancer, we must ensure that medical research remains a national priority for our policymakers. Notably, the return on the federal investments in medical research has been extraordinary. For example, in the last 40 years, U.S. patients with cancer have collectively gained nearly 14 million years of life because of NCI-funded cancer research. Therefore, AACR urges Congress to continue to support robust, sustained, and predictable annual increases in the budgets of NIH and NCI, and to provide consistent and sufficient annual funding for the Cancer Moonshot, FDA, and Centers for Disease Control and Prevention (CDC). These actions will further advance the frontiers of cancer science and medicine and save more lives from cancer.

Philip D. Greenberg, MD, FAACR
AACR President

Margaret Foti, PhD, MD (hc)
AACR Chief Executive Officer

Executive Summary

Unprecedented progress in medical research is increasing our understanding of the collection of diseases we call cancer and is driving remarkable improvements in cancer prevention, early detection, diagnosis, and treatment. These advances are made possible by investments in NIH, NCI, FDA, and CDC by the U.S. federal government. As the first and largest professional organization in the world dedicated to preventing and curing all cancers, AACR has been and continues to be a catalyst for scientific breakthroughs that save and enhance the lives of patients with cancer. AACR is also committed to increasing public understanding of cancer and advocating for increased federal funding for medical research.

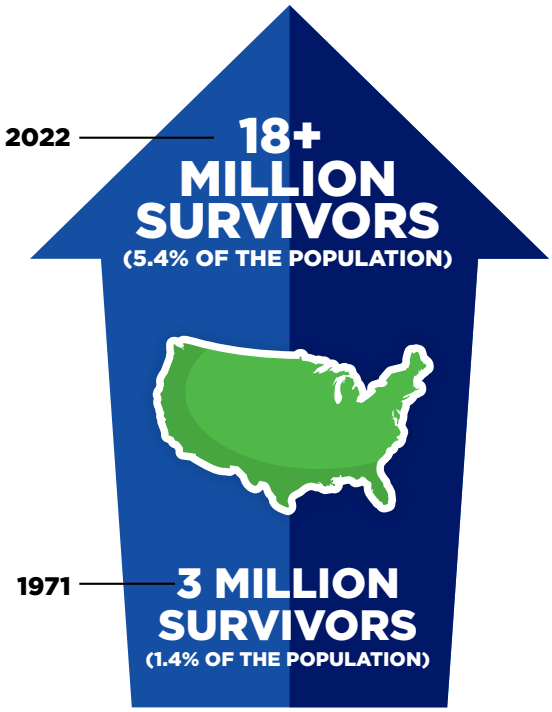
"All of the advances in cancer research are coming together to make therapies increasingly precise so we can improve the quality of life of patients."

Philip D. Greenberg, MD, FAACR
AACR President, 2023-2024

The annual AACR Cancer Progress Report to Congress and the American public is a cornerstone of AACR's educational efforts. This thirteenth edition of the report highlights how research continues to extend and improve the lives of Americans, including the lives of the eight courageous individuals featured in the report and their family members who have shared their experiences with cancer. It also underscores how unwavering, bipartisan support from Congress, in the form of robust and sustained annual increases in funding for NIH, NCI, FDA, and CDC, is urgently needed if we are to realize our vision of eradicating cancer for all populations.

Cancer in 2023

The remarkable progress being made against cancer is resulting in a steady reduction in cancer death rates, and a consistent rise in the number of people who live longer and fuller lives after a cancer diagnosis. In fact, the overall U.S. cancer death rate has fallen by 33 percent between 1991 and 2020, a reduction that translates into averting an estimated 3.8 million deaths from cancer. The reduction in overall cancer mortality is driven



largely by the decline in the U.S. lung cancer death rate, the pace of which has accelerated in recent years because of reduction in smoking and advances in early detection and treatment. Additionally, the reduction in death rates for melanoma, colorectal cancer, prostate cancer, and female breast cancer has contributed to the progress against overall U.S. cancer mortality. Notably, among U.S. children (14 years or younger) and adolescents (15 to 19 years), overall cancer death rates have declined by 70 percent and 64 percent, respectively, over the past five decades, driven largely by improvements in treatment.

Despite significant advances, cancer continues to be an ongoing public health challenge in the United States and around the world. In the United States alone, it is estimated that nearly 2 million new cancer cases will be diagnosed in 2023. Among the challenges we face is the fact that the advances we have made have not been uniform for all types and stages of cancer. For example, while the death rates for many of the commonly diagnosed cancers in the United States—including breast, lung, and prostate cancer—have been declining, those for other forms of cancer—most notably pancreatic and uterine cancer—have been increasing. Moreover, the burden of cancer is shouldered disproportionately by certain segments of the population, including racial and ethnic minorities and patients from other medically underserved populations. These disparities are driven by complex and interrelated factors, called social determinants of health.

In the United States, **patients with cancer** have collectively gained nearly 14 million years of life since 1980 as **a result of NCI-funded clinical trials**.

The burden of cancer and its economic toll, both on individuals and on the U.S. health care system, are expected to rise in the coming decades, underscoring the urgent need for more research to accelerate the pace of progress against cancer. The progress highlighted in this report was made as a direct result of the cumulative efforts of individuals working across the spectrum of medical research and the support from the federal government. Public sector funding from NIH and NCI directly contributes to patient benefit such as through the development of lifesaving anticancer therapeutics. Continued federal investments in NIH, NCI, FDA, and CDC will help the medical research community maintain the momentum of scientific and technological innovation, accelerate the pace of progress against cancer, and ensure that we achieve the President's Cancer Moonshot goal of reducing U.S. cancer death rates by 50 percent by the year 2047.

Understanding the Path to Cancer Development

Decades-long research in basic, translational, clinical, and population sciences, and the breakthroughs stemming from it, have advanced our understanding of cancer development. Insights gleaned from this knowledge have revealed cancer as a collection of diseases that are characterized by unchecked cell multiplication. We now understand that different cancer types share many so-called hallmarks or characteristics. These hallmarks are primarily acquired through alterations in the genetic material of normal cells. The nature and the type of genetic alterations determine when cancer is initiated, how fast it progresses, and where in the body it spreads.

Research has shown that there are two types of genetic mutations associated with cancer: inherited and somatic. Inherited mutations are passed on from parents to their progeny and contribute to about 10 percent of all cancer cases. Most cancers are caused by somatic mutations. Somatic mutations are acquired throughout a person's lifetime and can arise in multiple ways, including from errors made during cell division, smoking, certain viral infections, exposure to UV radiation, and/or exposure to mutagens or other cancer-causing chemicals.

Although cancer is a genetic disease at a fundamental level, transformation of normal cells into cancer cells, accumulation of cancer cells to form tumors, and spread of tumors to distant sites are all complex, multistep processes that are further influenced by changes outside the cell. As the disease progresses, cancer cells acquire additional characteristics that give them the ability to manipulate their cellular and molecular environment. The resultant tumor microenvironment can affect how the tumor grows and spreads, and cancer cells can reciprocally influence the tumor microenvironment to promote their survival.

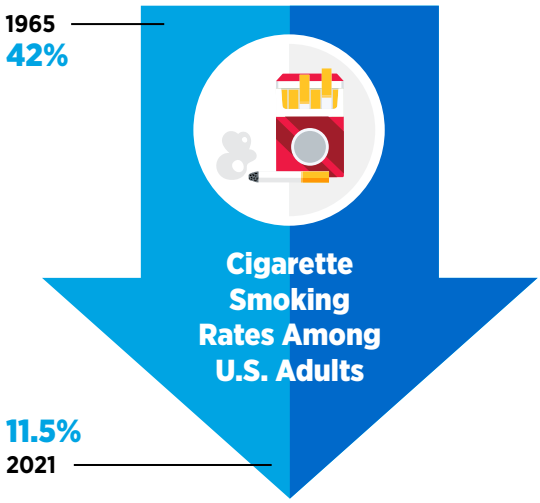
A technological revolution in our ability to study cancer at the levels of single cells and molecules has led to important insights, one of which is that each patient's cancer is unique, thus providing the basis for precision medicine. Also called personalized medicine, precision medicine is broadly defined as treating patients based on molecular characteristics that distinguish them from other individuals with the same disease. As ongoing research continues to unravel the mechanisms of cancer onset and progression, researchers are already leveraging existing knowledge to develop more effective, personalized anticancer therapeutics and improve health outcomes for patients with cancer.

Reducing the Risk of Cancer Development

Research in basic, translational, and population sciences has broadened our understanding of the factors that increase an individual's risk of developing cancer. Many of these risk factors are modifiable, such as reducing tobacco use, avoiding an

HALLMARKS OF CANCER CELLS

- **Spread to other parts of the body**
- **Multiply limitlessly**
- **Increase blood vessel formation toward tumor**
- **Evade the immune system**
- **Increase nutrient and oxygen supply to the tumor**
- **Escape cell death**
- **Grow uncontrollably**
- **Accumulate changes in the genetic material**



unhealthy diet, lowering physical inactivity, lowering exposure to UV radiation, limiting alcohol consumption, and preventing pathogenic infections. It is estimated that 40 percent of all cancer cases in the United States are attributable to preventable causes.

The development and implementation of public education and policy initiatives designed to eliminate or reduce exposure to preventable causes have reduced cancer incidence, morbidity, and mortality in the United States. Unfortunately, while the prevalence of some risk factors like tobacco use is on the decline, the rise in prevalence of other risk factors such as obesity threatens to reverse the significant progress against cancer that has been made in the last five decades. Therefore, it is essential that all stakeholders work together to enhance the dissemination of our current knowledge to reduce cancer risk and implement evidence-based policies and programs that minimize the incidence, morbidity, and mortality of cancer attributable to preventable causes.

Certain cancer risk factors are not always easy to avoid. These include carcinogens and pollutants encountered in the environment. Hormonal factors that result from normal physiology can also increase or decrease the risk of developing certain types of cancers. Furthermore, occupational or life stressors, such as chronic stress, lack of sleep, and night shift work, increase a person's risk of developing certain types of cancers.

As we learn more about environmental and occupational cancer risk factors and identify segments of the U.S. population who are exposed to these factors, new and equitable policies need to be developed and implemented to reduce cancer risk and improve the health of all populations.

Screening for Early Detection

Cancer screening means checking for the disease, or for abnormal cells that may become cancerous, in people who have no signs or symptoms of cancer. Cancer screening can help detect aberrations at the earliest possible stage during cancer development when they are successfully treatable, with a higher likelihood of being cured. The overarching goal of recommended screening is to reduce the burden of cancer at the population level.

Cancer screening recommendations are developed for individuals who are at an average or higher-than-average risk of being diagnosed with cancer. Key considerations that determine who should receive screening and for which cancer include gender and age, as well as genetic, environmental, behavioral, and social influences.

In the United States, the U.S. Preventive Services Task Force (USPSTF)—an independent, volunteer panel of national experts in disease prevention and evidence-based medicine—has recommendations for individuals who are at an average risk of being diagnosed with breast, cervical, colorectal, or prostate cancer. The USPSTF recommends that people who currently smoke or have a history of smoking, i.e., individuals who are at a high risk of being diagnosed with the disease, receive lung cancer screening.

Despite the evidence that cancer screening saves lives, systemic and structural barriers disproportionately limit the access of medically underserved populations to routine cancer screening. Researchers are using evidence-based interventions—such as comprehensive public health campaigns and culturally tailored strategies—to reduce these barriers, but more work is needed to ensure that all eligible individuals have equitable access to routine cancer screening and follow-up testing if findings of the screening test are abnormal.

Use of artificial intelligence (AI) to aid clinicians in cancer detection, and of liquid biopsy to detect multiple types of cancer from a single test, is an exciting new frontier that holds enormous potential for improving early detection of cancer. In recent years, FDA has approved several AI-assisted medical devices to aid clinicians in cancer diagnosis. However, a cautious approach to using AI in cancer care is warranted to avoid exacerbating inequities that can result from the fact that much of the data used to train current AI-driven models

In May 2023, USPSTF issued a draft **recommendation for breast cancer screening, lowering the age** of eligible individuals from 50 to 40. Researchers estimate that the revised recommendation could save 19 percent more lives **from breast cancer**.

lacks diverse and proportional representation of the patient population. Similarly, although liquid biopsy-based tests using the existing specimens from patients with cancer have shown the great potential of this approach for early detection, large prospective studies must demonstrate that screening using these tests can extend lives before these tests can be used in the clinic for simultaneous detection of multiple cancers.

Advancing the Frontiers of Cancer Science and Medicine

The dedicated efforts of individuals working in medical research fuel advances across the clinical cancer care continuum that are improving survival and quality of life for people around the world. Surgery, radiotherapy, and cytotoxic chemotherapy are three of the five main pillars of cancer treatment. However, these therapies can have long-term adverse effects on patients. Through ongoing clinical trials, researchers are evaluating whether less aggressive surgery, radiotherapy, and cytotoxic chemotherapy can be appropriate for some patients, allowing them to experience improved quality of life without adverse effect on their long-term survival.

Among the advances made from August 1, 2022, to July 31, 2023, are the 14 new anticancer therapeutics approved for use by FDA. During this period, FDA also approved two new optical imaging agents to help visualize cancerous tissue and new uses for 12 previously approved anticancer therapeutics.

Despite many advances across all pillars of cancer treatment, **patients from racial and ethnic minorities and other underserved populations** are **less likely to receive** the **standard of care** recommended for the type and stage of cancer with which they have been diagnosed.

Seven of the new anticancer therapeutics approved by FDA target specific molecules involved in cancer development and are referred to as molecularly targeted therapeutics. They are part of the precision medicine revolution in cancer care that is improving the lives of numerous patients. Among these treatments is the first folate receptor alpha (FRα) targeted therapeutic, mirvetuximab soravtansine-gynx (Elahere) that was approved for patients with ovarian cancer, such as **Jaclyn (Jackie) Vanraaphorst**, p. 88. Among the FDA expansions of previously approved therapy is the combination of HER2-targeted therapeutics, tucatinib (Tukysa) and trastuzumab (Herceptin), a new and first of a kind treatment option for certain patients with colorectal cancer, such as **Brian Beck**, p. 92.

In the 12 months from August 1, 2022, to July 31, 2023, FDA also approved several molecularly targeted therapeutics for patients with rare forms of cancer, including certain bile duct cancers and hematologic cancers.

SPOTLIGHT

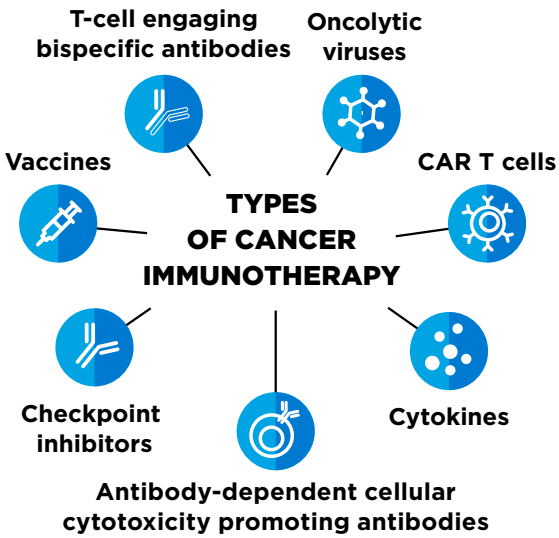
Immunotherapy: Pushing the Frontier of Cancer Medicine

Cancer immunotherapeutics work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens, like the virus that causes flu and the bacterium that causes strep throat. Not all immunotherapeutics work in the same way.

Over the past decade, cancer immunotherapy has emerged as one of the most exciting new approaches to cancer treatment. This is, in part, because some patients with metastatic disease who have been treated with these revolutionary anticancer treatments have had remarkable and durable responses, raising the possibility that they might be cured. It is also because some of the immunotherapeutics have been shown to work against an increasingly broad array of cancer types.

Immune checkpoint inhibitors (ICIs) are a class of immunotherapeutics that can release the brakes on T cells and trigger T cells to destroy cancer cells. The first ICI, ipilimumab (Yervoy), was approved by FDA in 2011 for the treatment of patients with metastatic melanoma. Since then, the use of ICIs has expanded rapidly, and these revolutionary new therapeutics have transformed the landscape of cancer treatment.

As of July 31, 2023, the FDA has approved 11 ICIs, and there is at least one ICI approved for treating 20 cancer types and for treating any type of solid tumors that share certain molecular characteristics. Just in the 12 months covered in this report, between August 1, 2022, and July 31, 2023, FDA approved two new ICIs, tremelimumab (Imjudo) and retifanlimab-dlwr (Zynyz), for the treatment of patients with a certain type of liver cancer and a rare form of skin cancer. During the same



period, FDA also expanded the use of a previously approved ICI, atezolizumab (Tecentriq), for the treatment of patients including children and young adults with alveolar soft part sarcoma, such as **Isabella (Bella) Snow Fraser**, p. 110, and **Alexis Browning**, p. 112.

CAR T-cell therapy is designed to dramatically increase the number of cancer-killing T cells a patient has, thereby boosting the immune system's ability to seek and destroy cancer cells. The first CAR-T cell therapy was approved in 2017 for the treatment of children and young adults with acute lymphoblastic lymphoma, such as **Cayden Addison**, p. 114. As of July 31, 2023, the FDA has approved six distinct CAR T-cell therapies for the treatment of a range of hematologic cancers.

T-cell engaging bispecific antibodies are another type of immunotherapy that works by bringing cancer-killing T cell in close proximity to the cancer cells. Between August 1, 2022, and July 31, 2023, FDA approved four new T-cell engaging bispecific antibodies for the treatment of patients with multiple myeloma, such as **Cindy Brown**, p. 122, and several additional hematologic cancers.

Cytokines, such as interferon-alpha (IFNα), are molecules that are released by immune cells, and can boost the cancer-killing function of the immune system. The December 2022 FDA approval of nadofaragene firadenovec-vncg (Adstiladrin), an interferon-based cancer immunotherapy, was a major advance in the treatment of patients with bladder cancer such as **Lesa Kirkman**, p. 118.

Despite the significant advances that have been made, only a small number of patients who are treated with an FDA-approved immunotherapeutic respond to the treatment. There are disparities in the access to these cutting-edge treatments. In addition, the current FDA-approved immunotherapeutics are not effective against all types of cancer. Identifying ways to increase the number of patients for whom treatment with an immunotherapeutic yields a remarkable and durable response is an area of intensive basic and clinical research investigation.

The new frontier of cancer immunotherapy, which includes preventive and therapeutic vaccines, innovative cell therapies, novel checkpoint inhibitors, and a new age of treatment combinations, is poised to transform the future of clinical cancer care.

Supporting Cancer Patients and Survivors

Unprecedented advances in cancer treatments over the past decade have led to more patients living longer and fuller lives after a cancer diagnosis. As of January 2022, the most recent year for which such data are available, there are more than 18 million people living with a history of a cancer diagnosis, which equates to about five percent of the U.S. population. This is a significant improvement from 50 years ago when cancer survivors constituted only 1.4 percent of the U.S. population. The number of survivors is expected to grow to 26 million by 2040. Understanding and addressing the short- and long-term challenges faced by cancer survivors, supporting their quality of life, and ensuring that care is accessible and equitable are important priorities in cancer survivorship research.

Cancer survivors are individuals who receive a diagnosis of cancer, beginning from when they are diagnosed through the balance of their lives. Survivors often face physical, psychosocial, and financial challenges, both during and after the conclusion of treatment; some continue to receive treatment indefinitely to manage their cancer. These challenges also extend to friends and family members who often act as informal caregivers. Health-related quality of life is increasingly being assessed by researchers in the development of new therapies and in clinical trials using patient reported outcomes. Understanding these challenges as well as how to reduce or eliminate them is an active area of research and continues to evolve as new therapies are discovered and used in the clinic.

Researchers are exploring ways to utilize palliative care, psycho-oncology, and other evidence-based strategies to improve quality of life for survivors of cancer. Engaging in physical activity, eliminating tobacco use, and eating a healthy diet have all been shown to improve the survivorship experience and improve cancer outcomes. Ongoing research is investigating the potential of new technologies, such as wearable devices, and innovative interventions, such as coordinated care, that may improve quality of life and meet the personalized needs of cancer survivors and their caregivers.

Envisioning the Future of Cancer Science and Medicine

Advances against cancer are driven by research, which provides the foundational knowledge of cancer onset and progression. This knowledge is essential to develop better ways to predict, prevent, diagnose, and treat cancer, as well as to enact evidence-based policies that improve public health.

As we envision a future where the success of treating all cancers is higher, and where the likelihood of a cure is possible, researchers, including **AACR President, 2023-2024, Philip D. Greenberg, MD, FAACR**, p. 104, are excited that the advances in discovery science, and the technologies that enable it, are opening exciting new frontiers in cancer science and medicine that will continue to benefit patients with cancer.

Researchers are using applications of powerful new technologies—such as the ability to study molecular changes in every cell of the tumor, the ability to visualize single molecules inside the cancer cell through simple chemical reactions, the ability of AI to analyze large datasets, or the ability of wearables to aid patient reported outcomes—to classify tumors at a molecular level, understand tumor heterogeneity, diagnose primary and metastatic cancers, develop better and more specific drugs, characterize treatment responses, track how cancer evolves over time, and predict overall survival.

Another frontier in cancer research is developing successful treatment for currently intractable cancers, such as pancreatic cancer and glioblastoma. Clinical studies are evaluating the potential of innovative anticancer therapeutics in treating cancers that have been difficult to tackle. Similarly, contributions of the human gut microbiome in modulating the response to cancer treatment, as well as findings that the human gut microbiome may help reduce the risk of developing cancer, are being investigated in multiple clinical studies, findings of which have the potential to revolutionize future cancer treatment and care.

Advancing the Future of Cancer Research and Patient Care Through the Adoption of Evidence-based Policies

Continued investment in medical research through NIH and NCI is essential for making progress against all aspects of cancer, including prevention, early detection, and treatment. These investments are not possible without the support of key members of Congress, whose efforts have ensured eight consecutive years of funding increases for NIH. While these additional investments have led to great strides in cancer research, many unmet needs remain.

For the medical research enterprise to reach its full potential, additional resources for NIH and NCI are necessary to support early-career researchers and to include patients from diverse backgrounds in clinical trials, which could help address cancer disparities. Further federal investments are necessary for cancer screening and prevention programs because approximately 40 percent of cancer cases in the U.S. can be attributed to preventable risk factors, such as tobacco use and exposure to UV radiation. In particular, the increasing use of e-cigarettes among adolescents demands greater understanding of the tobacco marketplace and stronger restrictions on tobacco products. Additionally, because patients are living longer due to advances in treatment, it is also taking longer to determine if these new drugs are safe and effective; FDA has recently published new guidance to improve the quality of clinical trials and timely drug development. FDA is also responding to record levels of drug shortages to ensure that approved drugs remain available to patients.

AACR Call to Action

Eight consecutive years of funding increases for medical research have contributed to the development of breakthrough therapies, as well as improvements in cancer prevention and screening, leading to a steady decline in U.S. cancer death rates for both men and women. With the number of cancer survivors continuing to grow, Congress cannot afford to reduce investments in cancer research and support for patients with cancer. Lawmakers must enact legislation to improve the quality of life for survivors by supporting patient navigation services and aiding in survivors' transition back to primary care. Furthermore, an increase in investments in medical research will expand access to a new generation of therapies that can transform cancer treatment and help patients with cancer live longer, healthier lives. Policymakers must continue to provide robust, sustained, and predictable funding increases for NIH to ensure greater availability of promising cancer treatments and to amplify cancer prevention and screening measures.

Therefore, AACR urges Congress to:

- **Increase the FY 2024 base budgets** of the NIH and NCI by at least $3.465 billion and $2.6 billion, respectively, for total funding levels of $50.924 billion for NIH and $9.988 billion for NCI.
- **Provide $1.7 billion in dedicated funding** for Cancer Moonshot activities in FY 2024 across NCI, FDA, and CDC with the assurance that Moonshot funding will supplement rather than supplant NIH funding in FY 2024.

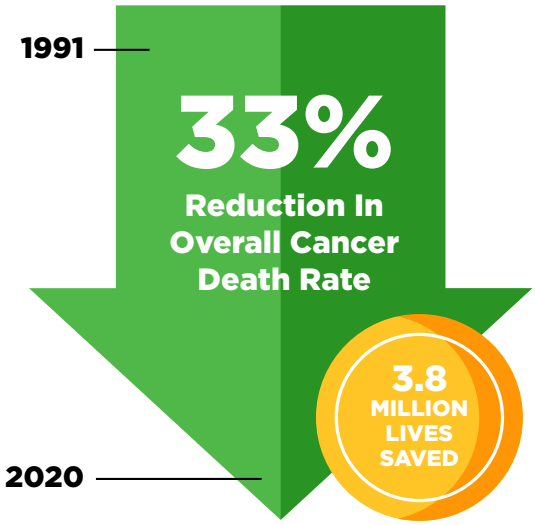
- **Appropriate at least $472.4 million** in FY 2024 appropriations for the CDC Division of Cancer Prevention to support comprehensive cancer control, central cancer registries, and screening and awareness programs for specific cancers.

- **Allocate $50 million in funding** for the Oncology Center of Excellence at FDA in FY 2024 to provide regulators with the capable staff and necessary tools to conduct expedited review of cancer-related medical products.

In summary, if we are to achieve the Cancer Moonshot goal of ending cancer as we know it, it will require robust funding for NIH and NCI biomedical research programs, as well as significant budget increases for FDA and CDC. If Congress follows through on these recommendations, we will improve our nation's health, including the lives of patients with cancer, and sustain our leadership in cancer research and medical science.

Scan the QR code
to watch a video summary
of the report

A Snapshot of a Year in Progress



Between August 1, 2022, and July 31, 2023, FDA approved:

- **14** **New anticancer therapeutics** that are now benefiting patients with various types of cancer
- **12** **Previously approved anticancer therapeutics** for treating new types of cancer
- **2** **New imaging agents**

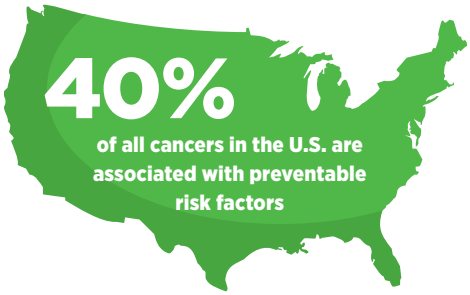
Research continues to power precision medicine, including:

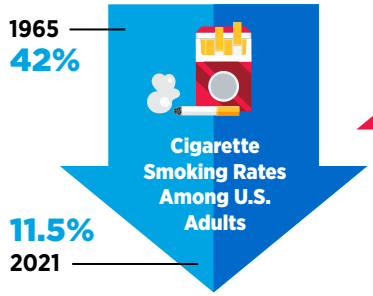
- A **first-in-class antibody drug conjugate** for patients with **ovarian cancer**.
- First approval of **a combination of two HER2 targeted therapeutics** to treat patients with metastatic **colon cancer**.
- A **new KRAS-targeted therapeutic** for advanced or metastatic **lung cancer**.
- A **new gene therapy-based immunotherapeutic** for certain patients with **bladder cancer**.
- The first approval of **an immune checkpoint inhibitor** for pediatric and adult patients with a **rare form of sarcoma**.
- **Four new T-cell engaging bispecific antibodies** for patients with **hematological malignancies**.

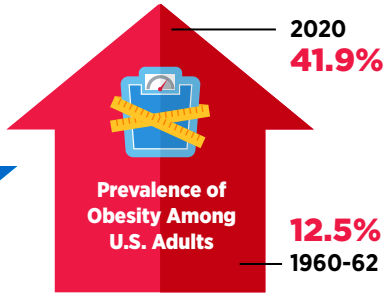
FDA APPROVALS IN TWO KEY CLASSES OF IMMUNOTHERAPEUTIC (As of July 31, 2023)

- **11 Immune Checkpoint Inhibitors** to treat 20 types of cancer and any cancer with certain molecular features.
- **6 CAR T-cell therapies** to treat a range of blood cancers.

Reducing the Risk of Cancer







Cancer Inequities in the United States

HIGHER cancer death rates	**From 2018 to 2020:** • **Black women** had 1.4 times and two times **higher death rates for breast and uterine cancer**, respectively, compared to White women, despite having similar incidence rates. • **American Indian** and **Alaska Native men** had 1.8-, 2.1-, and 2.7-times **higher death rates due to cancers** of the **kidney, liver, and stomach**, respectively, compared to White men. • **Hispanic men and women** had twofold **higher death rates for stomach cancer**, compared to White men and women.
2-FOLD or higher	Compared to cisgender patients, **transgender patients** have twofold or higher **increased risk of death** from non-Hodgkin lymphoma, prostate cancer, and bladder cancer.
78% higher	Among **older adults** with newly diagnosed cancer, **rural residents** have a 78 percent **higher one-year mortality** compared to urban residents.

New Frontiers in Cancer Science and Medicine

Researchers are hopeful that advances in discovery science, and technologies that enable it, will lead to a future where the success of treating all cancers is higher, and where the likelihood of a cure is possible.

- **Single-cell genomics** to understand molecular changes in every cell of the tumor
- **Microbiome modulation** to improve treatment responsiveness.
- **Cancer vaccines** to personalize treatment for each patient.
- **Artificial Intelligence** to aid in cancer detection and diagnosis.
- **Liquid biopsy** to detect multiple cancer types from a single test.

Screening for Early Detection

In May 2023, USPSTF issued a draft recommendation for breast cancer screening:

CANCER TYPE	PREVIOUS	DRAFT
	50 years	40 years

Researchers estimate that the revised recommendation could save 19 percent more lives from breast cancer.

AACR Call to Action

To improve our nation's health, including the lives of patients with cancer, and sustain our leadership in cancer science and medicine, AACR urges Congress to prioritize funding medical research by providing the following appropriations in FY 2024:

NIH	NCI	CDC's Division of Cancer Prevention and Control	FDA's Oncology Center of Excellence
$50.924 BILLION	$9.988 BILLION	$472.4 MILLION	$50 MILLION

Cancer in 2023

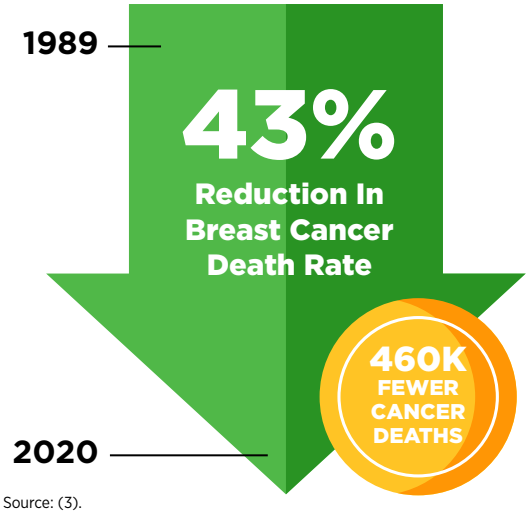
IN THIS SECTION, YOU WILL LEARN:

- In the United States, the overall cancer death rate has been steadily declining since the 1990s, with the reductions between 1991 and 2020 translating into more than 3.8 million cancer deaths avoided.
- The decline in overall U.S. cancer death rates is driven by steady declines in mortality from cancers of the breast, colon and rectum, lung, and prostate.
- More than 18 million cancer survivors were living in the United States as of January 1, 2022.
- Progress has not been uniform against all cancer types or all subtypes and stages of a given cancer type.
- There are stark inequities in the cancer burden among many sociodemographic groups within the United States; these inequities occur across the cancer continuum and are driven largely by social factors.
- The economic burden of cancer both on individuals and the U.S. health care system is expected to rise in the coming decades, highlighting the urgent need for more research to accelerate the pace of progress against cancer.

Research: Driving Progress Against Cancer

Research is the backbone of progress against cancer because it is the driving force behind every breakthrough that enhances survival and quality of life and every new policy or program designed to improve public health. Discoveries across the major areas of cancer research, including basic, clinical, translational, and population sciences, provide the foundation for advances in cancer prevention, detection, diagnosis, treatment, and survivorship.

Every clinical advance as well as every policy that spurs progress against cancer is the culmination of a complex process that requires collaboration over the course of many years among numerous different stakeholders committed to fundamentally changing the face of this devastating disease (see **Sidebar 1**, p. 13).



Source: (3).

The remarkable advances being made against cancer—in particular, improvements in prevention, early detection, and treatment—are resulting in a steady decline in U.S. cancer death rates year after year. In fact, the age-adjusted overall cancer death rate has fallen by 33 percent between 1991 and 2020, a reduction that translates into averting an estimated 3.8 million deaths from cancer (2). The reduction in overall U.S. cancer mortality rate is driven largely by the decline in lung cancer death rate, the pace of which has accelerated in recent years because of reduction in smoking and advances in early detection and treatment (see **Figure 1**, p. 14). Reduction in death rates for melanoma, colorectal cancer, prostate cancer, and female breast cancer has also contributed to overall progress against U.S. cancer mortality (2).

Research-driven advances in treatment are reflected in the steady declines in death rates for melanoma, leukemia, and kidney cancer (2). The death rate for chronic myeloid leukemia (CML), a cancer of the blood and bone marrow, for instance, has declined by 70 percent between 1975 and 2020 (5). This progress can be attributed to groundbreaking basic research discoveries from the 1960s through 1980s that identified the mechanistic underpinnings of the disease and propelled the development of a cascade of new treatments for CML (see **Sidebar 6**, p. 28) (6).

SIDEBAR 1

The Medical Research Community: Driving Progress Together

Progress against cancer can be accelerated when all stakeholders dedicated to fundamentally changing the burden of cancer work together. Further increasing collaboration will invigorate future breakthroughs. The key stakeholders are:

Adapted from (1).

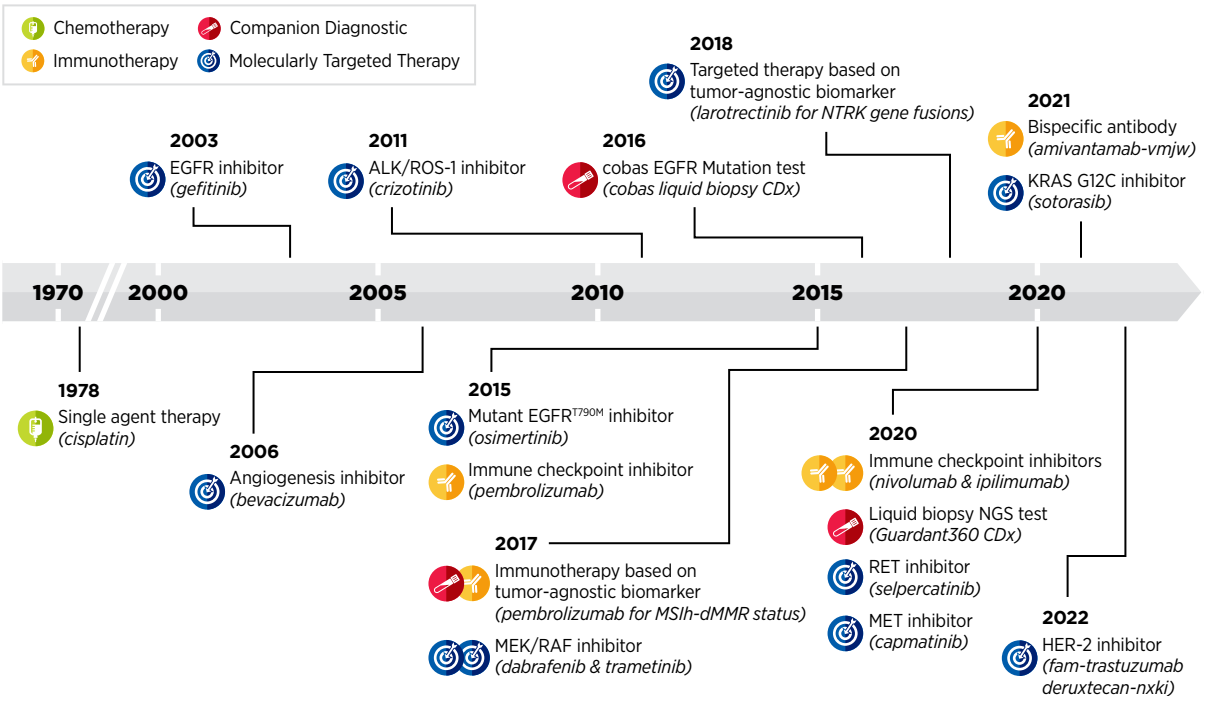
Among children (14 years or younger) and adolescents (15 to 19 years), overall cancer death rates have declined by 70 percent and 64 percent, respectively, between 1970 and 2020, driven largely by improvements in treatment (2).

Among the major advances made across the clinical cancer care continuum from August 1, 2022, to July 31, 2023, are 14 new anticancer therapeutics approved for use by FDA (see **Table 3**, p. 77). During this period, FDA also approved new uses for 12 previously approved anticancer therapeutics (see **Table 3**, p. 77), two agents to improve quality of life for patients with cancer undergoing active treatment, two new imaging agents to help visualize cancerous cells during surgery (see **Visualizing Lung Cancers More Precisely During Surgery**, p. 78 and **Imaging Prostate Cancer More Clearly**, p. 82), and several artificial intelligence-based tools to improve detection and diagnosis of cancers (see **Sidebar 24**, p. 66). Collectively, advances such as these are helping increase the number of

FIGURE 1

Research Driving Progress Against Lung Cancer

FIRST FDA APPROVALS OF THERAPEUTICS WITH UNIQUE MECHANISMS OF ACTION



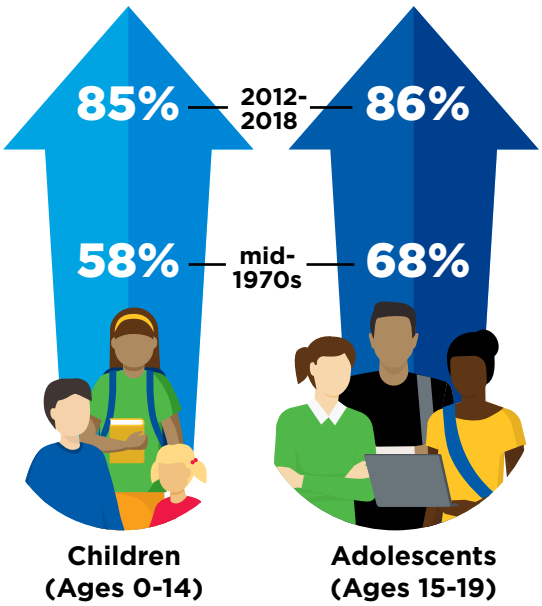
Discoveries over the past three decades have identified numerous cellular pathways that drive lung cancer development. Among these are alterations, also referred to as mutations (see **Sidebar 7**, p. 30), in genes such as Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), epidermal growth factor receptor (*EGFR*), fibroblast growth factor receptor (*FGFR*), anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), rearranged during transfection (*RET*), mesenchymal-epithelial transition factor (*MET*), neurotrophic tropomyosin receptor kinase (*NTRK*), and human epidermal growth factor receptor 2 (*HER2*). Research has also shown that cancer cells evade destruction by the immune system because they have high levels of proteins that can attach to and trigger brakes on immune cells, stopping them from attacking cancer cells. Collectively, these discoveries have laid the foundation for the development of molecularly targeted therapeutic and immunotherapeutic agents, many of which have yielded remarkably lasting responses for patients with lung cancer. Indicated on the timeline are the first FDA approvals for lung cancer of molecularly targeted therapeutics, novel diagnostic agents, and immunotherapeutics with a unique mechanism of action. Thanks to these clinical breakthroughs along with steep reduction in U.S. smoking rate, lung cancer mortality is declining rapidly. In fact, **the decrease in lung cancer mortality per year accelerated from 0.9 percent between 1995 and 2005 to 2.4 percent between 2005 and 2014 to nearly five percent between 2014 and 2020** (2,4).

children and adults who live longer and fuller lives after a cancer diagnosis. As of January 1, 2022, the most recent date for which such estimate is available, more than 18 million individuals with a history of cancer were alive in the United States (7). Recent studies indicate that the number of U.S. individuals living despite being diagnosed with metastatic disease has increased since the 1990s and this number is estimated to grow considerably in the coming years (8). This increase is attributable to the advances in treatments that are available for patients with metastatic cancers.

Cancer: An Ongoing Public Health Challenge

Although incredible progress has been made against cancer, it continues to be an enormous public health challenge in the United States and around the world (see **Sidebar 4**, p. 22). In the United States alone, an estimated 1,958,310 new cases of cancer will be diagnosed in 2023 and 609,820 people will

5-YEAR RELATIVE SURVIVAL RATE
(All cancers combined)



Source: (2).

die from the disease (see **Table 1**, p. 16). Men have a higher incidence of many cancer types, including bladder, colon, and brain cancer compared to women and ongoing research is evaluating the role of a range of biological factors including genetics, epigenetics, metabolism, and immunity in mediating these differences.

Unfortunately, many population groups in the United States experience a disproportionately high rate of cancer incidence and death attributable largely to socioeconomic disadvantages. It should also be noted that current estimates of cancer burden do not reflect the adverse impact of COVID-19, which caused serious declines in screening, early detection, and new cancer diagnoses, and which continues to take a toll on cancer care especially among the medically underserved populations (9-11). Ongoing monitoring of cancer-related population-based data is warranted to assess the long-term consequences of COVID-19 on cancer burden in the United States.

Inequities in the Burden of Cancer in the United States

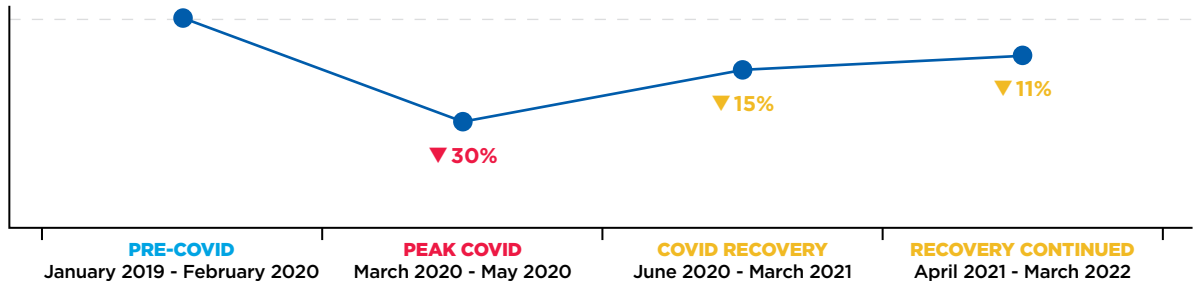
While we are making unprecedented advances against cancer, the grim reality is that these advances have not benefited everyone equally. Because of a long history of structural inequities and systemic injustices in the United States, certain segments of the population continue to shoulder a disproportionate burden of adverse health conditions, including cancer.

Cancer disparities are one of the most pressing public health challenges in the United States. The National Cancer Institute (NCI) defines cancer disparities as adverse differences in cancer, such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (see **Sidebar 2**, p. 17).

As outlined in the *AACR Cancer Disparities Progress Report 2022* (13), racial and ethnic minorities and other medically underserved U.S. populations shoulder a disproportionately higher burden of cancer (see **Sidebar 3**, p. 18).

Individuals who are Black have the highest death rates and lowest survival rates of any racial or ethnic group in the U.S. for most cancers, largely driven by structural and systemic inequities (14). While the disparity in the overall cancer death rate between Black and White populations has narrowed by half over the last two decades, Black individuals still had a 12 percent higher overall cancer death rate compared to White individuals, and the highest death rate from cancer among all U.S. racial or ethnic groups in 2020 (5). American Indian and Alaska Native (AIAN) individuals are a culturally and geographically diverse U.S. population group who experience a disproportionally high prevalence of several chronic illnesses, including many cancers, largely because of

AVERAGE NUMBER OF NEW CANCER DIAGNOSES DURING THE COVID-19 PANDEMIC
(For eight cancer types combined)



Source: (12).

TABLE 1

Estimated Incidence and Mortality* for Selected Cancers

	ESTIMATED 2023 INCIDENCE			ESTIMATED 2023 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	1,958,310	1,010,310	948,000	609,820	322,080	287,740
Head and Thorax Region						
Breast	300,590	2800	297,790	43,700	530	43,170
Tongue	18,040	13,180	4860	2940	1950	990
Mouth	14,820	8680	6140	3090	1870	1220
Pharynx	20,070	16,340	3730	4140	3260	880
Other oral cavity	1610	1090	520	1410	1060	350
Larynx	12,380	9900	2480	3820	3070	750
Lung and bronchus	238,340	117,550	120,790	127,070	67,160	59,910
Eye and orbit	3490	1900	1590	430	240	190
Brain and other nervous system	24,810	14,280	10,530	18,990	11,020	7970
Gastrointestinal (GI) System						
Esophagus	21,560	17,030	4530	16,120	12,920	3200
Stomach	26,500	15,930	10,570	11,130	6690	4440
Small intestine	12,070	6580	5490	2070	1170	900
Colon & rectum	153,020	81,860	71,160	52,550	28,470	24,080
Anus, anal canal, & anorectum	9760	3180	6580	1870	860	1010
Liver and intrahepatic bile duct	41,210	27,980	13,230	29,380	19,000	10,380
Gallbladder and other biliary	12,220	5750	6470	4510	1900	2610
Pancreas	64,050	33,130	30,920	50,550	26,620	23,930
Skin (excluding basal and squamous)						
Melanoma of the skin	97,610	58,120	39,490	7990	5420	2570
Other nonepithelial skin	7320	4690	2630	4480	3060	1420
Urogenital System						
Uterine cervix	13,960	-	13,960	4310	-	4310
Uterine corpus	66,200	-	66,200	13,030	-	13,030
Ovary	19,710	-	19,710	13,270	-	13,270
Vulva	6470	-	6470	1670	-	1670
Vagina and other genital organs, female	8470	-	8470	1740	-	1740
Prostate	288,300	288,300	-	34,700	34,700	-
Testis	9190	9190	-	470	470	-
Penis and other genital organs, male	2050	2050	-	470	470	-
Urinary bladder	82,290	62,420	19,870	16,710	12,160	4550
Kidney and renal pelvis	81,800	52,360	29,440	14,890	9920	4970
Ureter and other urinary organs	4470	2810	1660	990	600	390
Endocrine System						
Thyroid	43,720	12,540	31,180	2120	970	1150
Hematologic System						
Acute lymphocytic leukemia	6540	3660	2880	1390	700	690
Chronic lymphocytic leukemia	18,740	12,130	6610	4490	2830	1660
Acute myeloid leukemia	20,380	11,410	8970	11,310	6440	4870
Chronic myeloid leukemia	8930	5190	3740	1310	780	530
Hodgkin lymphoma	8830	4850	3980	900	540	360
Non-Hodgkin lymphoma	80,550	44,880	35,670	20,180	11,780	8400
Myeloma	35,730	19,860	15,870	12,590	7000	5590
Other leukemia	5020	3280	1740	5210	3150	2060
Other Cancers						
Bones and joints	3970	2160	1810	2140	1200	940
Soft tissue (including heart)	13,400	7400	6000	5140	2720	2420

*Rounded to the nearest 10.

Source: Estimated new cases are based on 2005-2019 incidence rates reported by the North American Association of Central Cancer Registries (NAACCR). Estimated deaths are based on 2006-2020 U.S. mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention.

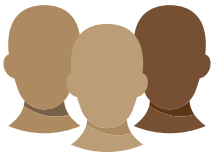
Table is modified from (28).

SIDEBAR 2

Which U.S. Population Groups Experience Cancer Disparities?

According to the National Cancer Institute, cancer disparities are adverse differences in cancer such as the number of new cases and deaths, cancer-related health complications, quality of life after cancer treatment, financial burden, screening rates, and stage at diagnosis that are shouldered by certain population groups including:

Individuals belonging to certain ancestry, racial or ethnic minority populations



Individuals of low socioeconomic status

Individuals who lack or have inadequate health insurance coverage

Residents in certain geographic locations, including rural areas

Individuals belonging to sexual and gender minorities

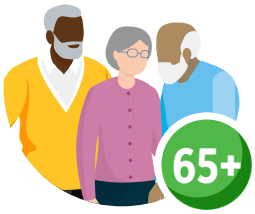
LGBTQ+

Immigrants, refugees, or asylum seekers

Individuals with disabilities

Adolescents and young adults

Older adults



Adapted from (13).

barriers to quality health care (15). Cancer is the leading cause of death in the U.S. Hispanic population, the second largest racial or ethnic group in the continental United States and Hawaii, whereas heart disease is the leading cause of death in the non-Hispanic White population (16).

Researchers are increasingly recognizing the heterogeneity in cancer burden among individuals within each of the major racial or ethnic minority groups (13). As one example, the U.S. Asian population has ancestry in numerous countries of origin and the Native Hawaiian or other Pacific Islander (NHOPI) population comprises more than 25 diverse subgroups with distinct variations in historical backgrounds, languages, and cultural traditions. Striking disparities in cancer death rates between NHOPI and Asian individuals have been identified since national death certificates included a new racial classification system which separated NHOPI individuals from Asian individuals, two populations that are frequently aggregated in cancer epidemiological data (17). These findings highlight the vital importance of disaggregated cancer data to fully understand cancer disparities and develop effective strategies for achieving health equity.

In addition to racial or ethnic minorities, many other segments of the U.S. population shoulder a disproportionate burden of cancer (see **Sidebar 2**, p. 17). These include residents in rural areas that lack access to cutting-edge cancer treatments and/or state-of-the-art health care facilities, sexual and gender minorities who experience bias and discrimination in health care settings, and low-income households where there is persistent poverty, and limited access to healthy food or the needed health care. It should

SIDEBAR 3

Cancer Inequities in the United States

Certain U.S. population groups (see **Sidebar 2**, p. 17) shoulder a disproportionate burden of cancer. Recent examples of disparate cancer incidence and outcomes are provided here. Disparities in other aspects of cancer care are highlighted in relevant sections throughout the report. A more in-depth discussion of cancer disparities and recent progress in addressing these inequities, as well as a call to action, is detailed in *AACR Cancer Disparities Progress Report 2022* (13).

HIGHER cancer death rates	**From 2018 to 2020:** • **Black women** had 1.4 times and two times **higher death rates for breast and uterine cancer**, respectively, compared to White women, despite having similar incidence rates; **Black men** had two times **higher death rates for prostate cancer**, compared to White men (17). • **American Indian** and **Alaska Native men** had 1.8-, 2.1-, and 2.7-times **higher death rates due to cancers** of the **kidney, liver, and stomach**, respectively, compared to White men (17). • **Native Hawaiian** or **other Pacific Islander** (NHOPI) 20- to 49-year-olds had the **highest cancer death rates**, compared to all other racial or ethnic groups of similar age range (17). • **Hispanic men and women** had twofold **higher death rates for stomach cancer**, compared to White men and women (17).
2-FOLD or higher	Compared to cisgender patients, **transgender patients** have twofold or higher **increased risk of death** from non-Hodgkin lymphoma, prostate cancer, and bladder cancer (18).
5-FOLD or higher	Among **childhood cancer survivors**, those **living in neighborhoods** with the highest **socioeconomic deprivation** are at a five-fold or higher **increased risk of all-cause deaths** compared to those living in the least socioeconomically disadvantaged neighborhoods (19).
LEAST progress	**Congressional districts** in the **U.S. Midwest** and **Appalachia** made the **least progress**, while those along the southern East Coast and the southern border made the greatest progress in **reducing overall cancer death rates** between 1996–2003 and 2012–2020 (20).
78% higher	Among **older adults** with newly diagnosed cancer, **rural residents** have a 78 percent **higher one-year mortality** compared to urban residents (21).

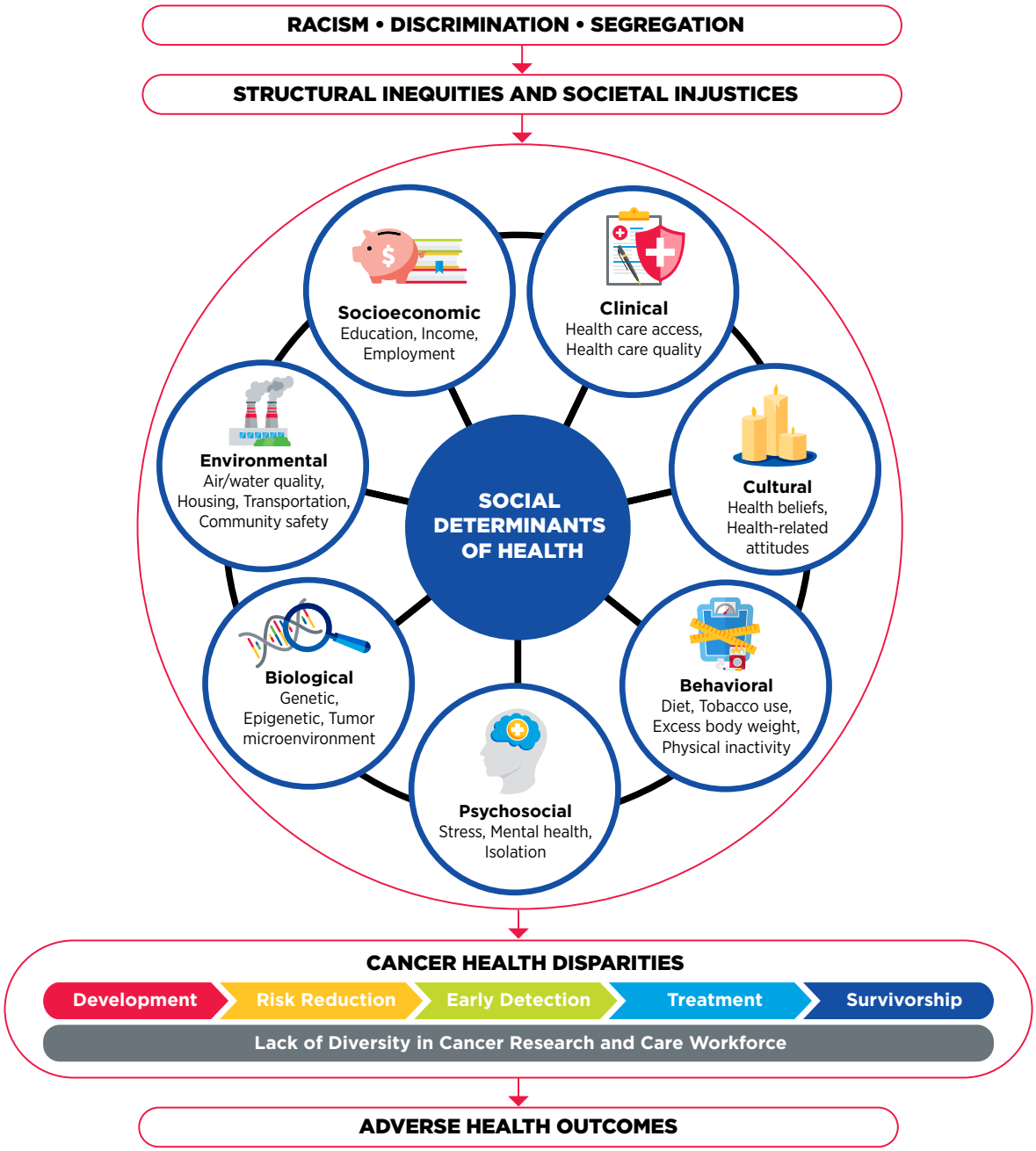
be noted that patients with intersectional identities often experience multilevel barriers to cancer care that adversely impact screening, diagnosis, treatment, and survivorship. As one example, recent data have shown that Black and AIAN populations living in rural areas experience greater poverty and lack of access to quality care, which expose them to greater risk of experiencing poor cancer outcomes (22).

Root causes of cancer disparities are multidimensional and multifactorial. Researchers have developed many models to understand and address health inequities. A key component of these models is the framework of social determinants of health (SDOH). According to NCI, SDOH are the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and grow older that can affect their health, well-being, and quality of life (see **Figure 2**, p. 19). It is increasingly evident that structural racism and systemic injustices are key adverse social factors, creating conditions that perpetuate health inequities, including cancer disparities, for racial or ethnic minorities and other medically underserved populations (23-26).

Considering that a significant proportion of the U.S. population is affected by cancer disparities, it is important

FIGURE 2

Social Determinants of Health



Complex and interrelated factors called social determinants of health (SDOH) are main drivers of cancer disparities. The National Cancer Institute defines SDOH as the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and grow older that can affect their health, well-being, and quality of life. These include economic policies and systems, development agendas, social norms, social policies, and political systems (27). In the United States, centuries of structural racism and systemic inequities have perpetuated and exacerbated adverse differences in SDOH for racial and ethnic minorities and other groups that are medically underserved. The circle in the figure depicts key SDOH and how they interconnect and intersect, both at societal and community levels and at the individual level. Selected examples of the multilevel factors comprising SDOH are highlighted. Collectively, these factors impact every stage of the cancer continuum, leading to worse health outcomes for people from groups that are racially, structurally, and/or economically disadvantaged.

that public health experts intensify efforts designed to improve the understanding and mitigation of these inequities. Only with new insights obtained through innovative and inclusive research, such as basic research using biospecimens from diverse populations, clinical studies involving participants from all sociodemographic backgrounds, and health care delivery research that is representative of everyone in the communities, will we be able to develop and implement interventions that eventually eliminate cancers for all populations.

Variable Progress Against Different Types of Cancer and Stages of Diagnosis

Among the current challenges in cancer science and medicine is the uneven progress against different cancer types and different stages of a given cancer type.

These challenges are illustrated by the fact that the 5-year relative survival rates for U.S. patients vary widely depending on both the type of cancer diagnosed and the stage at diagnosis (5). For example, the overall 5-year relative survival rates of 94 percent for patients with melanoma and 97 percent for patients with prostate cancer stand in stark contrast to the overall 5-year relative survival rates of 23 percent for those with liver cancer and 13 percent for those with pancreatic cancer. In addition, among women with breast cancer and men with prostate cancer, those whose cancer is confined to the breast, or to the prostate, have 5-year relative survival rates of 99 percent and 100 percent, respectively, while those whose cancer has metastasized have 5-year relative survival rates of 31 percent and 34 percent, respectively (5).

Variable progress among different cancer types can be partly attributed to the availability of novel cutting-edge therapeutic options, or lack thereof, that have moved rapidly from the laboratory to the clinic and are now available to patients. As one example, between January 1, 2011, and July 31, 2023, the U.S. Food and Drug Administration (FDA) approved five immunotherapeutics and six molecularly targeted therapeutics for use alone or in combination for the treatment of patients with metastatic melanoma, a previously intractable cancer. Thanks to these innovative new therapeutics, melanoma mortality rates have declined rapidly between 2011 and 2020 by about five percent per year in adults younger than age 50 and three percent per year in those 50 and older (28). In contrast, progress has been slow for patients with glioblastoma multiforme (GBM), an aggressive form of brain tumor (see **Tackling Difficult-to-Treat Cancers**, p. 147). Since the approval of the chemotherapeutic temozolomide nearly 25 years ago, no new anticancer agents have shown promise in improving overall survival. Consequently, the 5-year relative survival rate for patients with GBM remains at a dismal seven percent (29).

Developing new and effective methods for early detection of more cancer types could help address the challenge of variable progress between types of cancer because the likelihood of cure is much higher when cancer is diagnosed at an early stage while it is confined to its original location than when it has spread to distant sites. Additionally, intensive research into the molecular underpinnings of cancer initiation and progression is vital in order to improve future therapeutic options for currently hard-to-treat diseases (see **Tackling Difficult-to-Treat Cancers**, p. 147).

The Growing Population Burden of Cancer

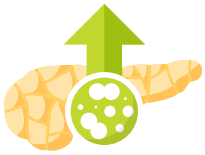
The public health challenges posed by cancer are predicted to grow considerably in the coming decades unless we develop and implement more effective strategies for cancer prevention, early detection, and treatment (30). In the United States alone, the number of new cancer cases diagnosed each year is expected to reach nearly 2.3 million by 2040 (30). This is because cancer is primarily a disease of aging; 57 percent of diagnoses occur among those 65 and older (28), and this segment of the U.S. population is expected to grow from 54.1 million in 2019 to nearly 81 million in 2040 (31).

Also contributing to the projected increase in the number of U.S. cancer cases are the high rates of obesity and physical inactivity and the continued use of cigarettes by 11.5 percent of adults (32). However, it should be noted that a significant proportion of lung cancers (16 percent in women and 10 percent in men) are diagnosed in individuals without a history of smoking (33) and there is a need for more research to determine whether the incidence rate of lung cancer among those without a history of smoking is increasing (34). Identification of risk factors, characterization of disease, and development of evidence-based early detection and treatments are critical needs to lower the burden of lung cancer in the population of patients who do not have a history of smoking.

While overall cancer incidence in the United States has stabilized in recent years, the incidence of certain cancer types such as pancreatic cancer and uterine cancer (5) is steadily increasing. Additionally, many recent studies have reported an increase in the incidence of colorectal cancer among individuals younger than 50 years, a phenomenon referred to as early-onset cancer (35,36). According to a recent report, between 2011 and 2019, the colorectal cancer incidence rate increased by 1.9 percent per year in people younger than 50 years (35). Many of the early-onset colorectal cancer cases are diagnosed at an advanced stage. Between 2010 and 2019, among 20- to 49-year-old individuals, incidence of advanced-stage colorectal cancer increased by about three percent per year (35).

Understanding the reasons behind rising cases of early-onset colorectal cancer is an area of intensive research. To reduce

Pancreatic cancer incidence rates are rising in the United States and increasing faster among **younger, particularly Black, women** than among men of the same age (38).



the burden of early-onset colorectal cancer, the United States Preventive Services Taskforce (USPSTF) and many professional societies have modified their screening guidelines to recommend starting colorectal cancer screening at an earlier age (see **Guidelines for Cancer Screening**, p. 58). Researchers are also evaluating new and improved strategies including genetic testing and other approaches for prevention and early detection of colorectal cancer in the younger population (37).

Another cancer for which U.S. incidence rate has been rising is cervical cancer (39,40). According to a recent analysis, the rate of advanced cervical cancer (that has spread to the bladder or rectum at diagnosis) increased by 1.3 percent per year from 2001 to 2018 (39). A second report showed that, among U.S. women ages 30 to 34 years, overall cervical cancer incidence increased by 2.5 percent per year between 2012 and 2019 (40). Considering that nearly all cervical cancers are caused by infection with human papillomavirus (HPV) and that HPV vaccination (see **Prevent and Eliminate Infection from Cancer-causing Pathogens**, p. 48) and cervical cancer screening are extremely effective in reducing the burden of the disease, these data emphasize the importance of public health measures to boost cervical cancer prevention and early detection in the United States (see **Screening for Early Detection**, p. 54).

The Global Burden of Cancer

Beyond the United States, cancer is an ongoing global challenge (see **Sidebar 4**, p. 22). According to a recent analysis, there were an estimated 17.2 million new cancer cases (excluding nonmelanoma skin cancer) and 10 million cancer deaths globally, in 2019 (41). The study evaluated cancer burden in terms of cancer-related deaths, as well as disability-adjusted life years (DALYs) and years of life lost (YLLs), which are two measures of cancer morbidity. Researchers found that among the 22 groups of diseases and injuries analyzed, cancer was second only to cardiovascular disease in the number of deaths, DALYs, and YLLs (41). The five leading causes of cancer-related morbidity among men and women combined were cancers of the lung, colon and rectum, stomach, breast, and liver.

There is a stark disparity in the cancer burden among countries with different levels of socioeconomic development. Researchers use various metrics such as human development index (HDI) or sociodemographic index (SDI), which are composite measures of social and economic development, to identify where countries or geographic areas fall on the spectrum of development. SDI quantification considers income per capita, average years of education, and total fertility rate for citizens younger than 25 (42); HDI measurement considers income per capita, average years of education, and life expectancy at birth (43). While age-adjusted cancer incidence and mortality rates are declining in countries with high SDI, both rates are still trending upward in lower SDI countries (41). Based on a recent estimate, between 2010 and 2019, countries with the lowest SDI experienced the largest percent increase in the numbers of cancer cases and deaths (41).

Considering the growth and aging of the global population and the negative impact of recent global crises such as the COVID-19 pandemic on cancer research and patient care (45), researchers caution that the burden of cancer worldwide may rise significantly in the coming decades. One area in which progress is urgently needed is the establishment of population-based cancer registries in all countries because the collection of high-quality cancer surveillance data is essential for developing effective national cancer control plans. Notably, only one in five low- and middle-income countries has the necessary data to drive policy and reduce the burden and suffering due to cancer, according to the International Agency for Research on Cancer (46).

Another emerging concern among public health experts is the dramatic rise since the 1990s in the incidence of early-onset cancers, including cancers of the breast, colon, esophagus, kidney, liver, and pancreas, among others, around the world (47). While improvements in early detection may be attributable, in part, to this rising cancer incidence, researchers hypothesize that early life exposures to certain cancer risk factors (see **Reducing the Risk of Cancer Development**, p. 38), including diets rich in highly processed foods, alcohol, sedentary lifestyle, obesity, environmental carcinogens, and an unfavorable microbiome, many of which have become more prevalent in recent decades, are playing a role in the increased incidence of early-onset cancers (47). Notably, 44 percent of cancer deaths worldwide are caused by modifiable risk factors, such as smoking and drinking alcohol (48).

To ensure equitable progress against cancer worldwide, it is imperative that the global medical research community work together and shares best practices to implement newer and more

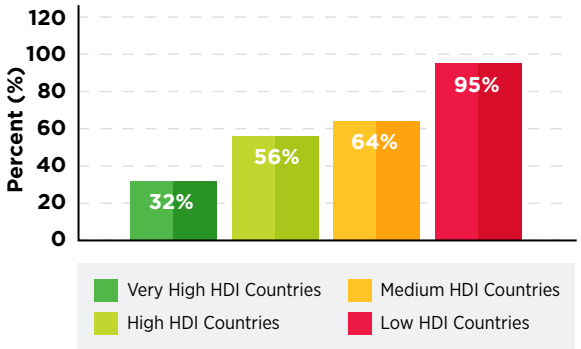
In high-income countries, most patients with cancer see a physician within a month of experiencing symptoms; **in low-income countries, this interval is 1.5 to 4 times longer** for most cancer types (44).

SIDEBAR 4

Global Burden of Cancer

Cancer is a major public health challenge worldwide, as reflected by the rising number of new diagnoses and deaths around the globe. The disparate burden of cancer based on the human development index (HDI) of a country (a composite measure of social and economic development that accounts for income per capita, average years of education, and life expectancy at birth) highlights key barriers to achieving global health equity. Examples included here offer a broad view of the global burden of cancer.

INCREASE IN ESTIMATED NEW CANCER CASES BETWEEN 2020 AND 2040



Source: (30).

Tracheal, bronchus, and lung cancers are the **leading causes of cancer deaths** (34).

Breast cancer is the **leading cause of cancer-related deaths among women** (41).

Diagnoses and deaths from colorectal cancer **more than doubled** over the past three decades (51).

Liver cancer is **among the top five causes of cancer death in 90 countries**; the number of new cases per year is predicted to increase by 55 percent between 2020 and 2040 (52).

Six percent of new cervical cancer cases in 2018 were diagnosed in women living with HIV and five percent were attributable to the HIV infection. **Eighty-five percent of women with cervical cancer and HIV live in sub-Saharan Africa** (53).

effective strategies that incorporate local needs and knowledge into tailored national cancer control plans. Public health experts have identified several priorities based on present and future needs of low resource countries, including reducing the burden of advanced cancers; improving access, affordability, and outcomes of treatment; utilizing value-based care; fostering implementation research; and leveraging technology to improve cancer control (49). The urgent need for robust worldwide investments in medical research is emphasized by recent findings that estimated the cumulative global economic burden of cancer to be at an enormous $25.2 trillion over the next 30 years (50).

Funding Cancer Research: A Vital Investment

Cancer exerts an immense toll, both because of the number of lives it affects each year and its significant economic impact. The direct medical costs of cancer care are one measure of the financial impact of cancer, and in the United States alone, these costs were estimated to be nearly $209 billion in 2020, the last year for which these data are currently available (28). Unfortunately, these numbers stand in stark contrast to the NCI budget of $6 billion for the same year. Notably, the direct medical costs do not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, which are also extremely high. As one example, the costs of lost productivity for U.S. adolescent and young adult patients with cancer (age 15 to 39) diagnosed in 2019 were an estimated $18 billion over their lifetime (54).

Patients with cancer shoulder a large amount of economic burden associated with cancer care. In 2019, in the United States, patients with cancer lost nearly $5 billion due to time costs—value of time that patients spend traveling to and from health care, waiting for care, and receiving care—and paid an estimated $16.2 billion in out-of-pocket costs for cancer care (55).

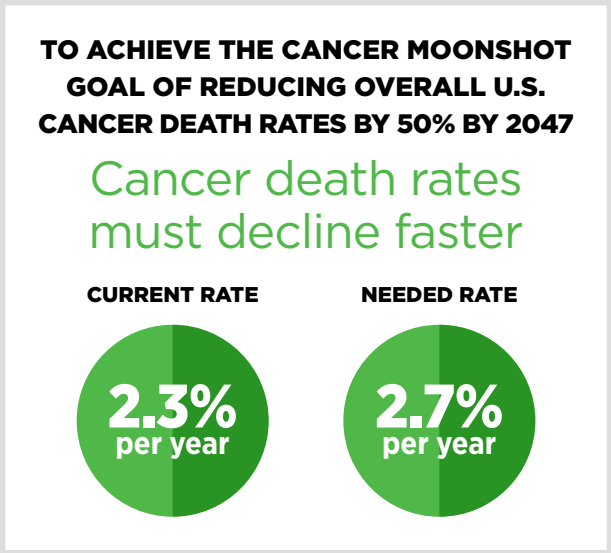
With the number of cancer cases projected to increase in the coming decades, it is likely that both the direct and indirect costs will also escalate. According to a recent report the economic burden of cancer in the United States will reach $5.3 trillion over the next three decades (50). The rising personal and economic burden of cancer underscores the urgent need for more research so that we can accelerate the pace of progress and curb the increasing burden of this disease.

Recent advances in cancer prevention, detection, and treatment, many of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers across the spectrum of cancer science and medicine. Much

of their work, as well as that of FDA and CDC, is supported by funds from the federal government. Public sector funding from NIH and NCI contributes significantly to the development of novel anticancer drugs including molecularly targeted therapeutics and immunotherapeutics (see **Advances in Treatment with Molecularly Targeted Therapy**, p. 83 and **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99) (56,57). The rapid pace of approval of these cutting-edge treatments, many of which were evaluated in NCI-funded clinical trials, has transformed the treatment landscape and dramatically improved patient outcomes. A recent study that evaluated the population-level impact of NCI-funded clinical research concluded that over the past 40 years, patients with cancer in the United States gained 14 million years of additional life because of these trials (58). Collectively, these findings highlight the importance of federal investments in medical research in saving and extending lives and driving progress against cancer.

The consecutive increases for the NIH budget in the last seven fiscal years have helped maintain the momentum of progress against cancer and other diseases (see **Investments in Research Fuel a Healthier Future**, p. 153). Additionally, NIH research grants help sustain the U.S. economy. In Fiscal Year (FY) 2022, the $36.68 billion awarded to researchers in the 50 U.S. states and the District of Columbia supported more than 568,000 jobs and nearly $97 billion in economic activity (59).

NCI's current success rate of 14.1 percent in FY 2021 has created a grant funding crisis and has left potentially lifesaving cancer science and medicine unfunded. There are also serious concerns that early-stage scientists and those from underrepresented racial or ethnic backgrounds might choose other career paths instead of academic research, which will impede progress against cancer.



If Congress lowers the NCI budget, it will force the Institute to reduce pay lines to even lower levels. Such actions will result in highly meritorious grants being unfunded and make it harder for the next generation of scientists to build promising careers in cancer research.

Therefore, it is imperative that in the years ahead, Congress continues to provide sustained, robust, and predictable increases in investments in the federal agencies that are vital for fueling progress against cancer, in particular, NIH, NCI, FDA, and CDC (see **AACR Call to Action**, p. 167). Such investments will help the medical research community sustain the momentum of scientific and technological innovation and accelerate the pace of progress against cancer to achieve the President's Cancer Moonshot goal of reducing U.S. cancer death rate by 50 percent by the year 2047.

Understanding the Path to Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- Cancer is a collection of diseases that are characterized by unchecked cell multiplication.
- Basic research is an essential driver of our understanding of the biology of cancer.
- Both acquired and inherited genetic mutations can contribute to cancer initiation and progression.
- Cancer development is influenced by modifications inside the cell as well as changes in the environment that surrounds a tumor.
- Technological advances are revolutionizing the identification of alterations in DNA, RNA, protein and cells that drive cancer.
- The knowledge gleaned from an integrated approach to understanding cancer development is fueling progress in the field of precision medicine.

Cancer is not a single disease but a collection of related diseases, in which some of the body's cells divide uncontrollably and spread to other parts of the body.

During the course of cancer development, abnormal or damaged cells acquire so-called "hallmarks" or characteristics that distinguish cancer cells from normal cells. Some of the hallmarks of cancer cells include their ability to: multiply limitlessly by ignoring signals that tell cells to stop dividing or to die; sustain rapid growth by relying on unique nutrients that are different from those used by normal cells; accumulate multiple changes in their genetic material; leave the tissue of origin and spread to other tissues; evade the immune system responsible for eliminating abnormal or damaged cells; and recruit blood vessels, thus increasing nutrients and oxygen supply to tumors (see **Figure 3**, p. 25) (62).

There are several ways to characterize cancers, and the methodology used depends on the type and purpose of the research and/or reporting (see **Sidebar 5**, p. 26). In most research and clinical settings, multiple classification methods are used simultaneously to identify and describe the type of cancer that a person has.

Research funding from NIH has contributed to the development of **354 out of 356 new drugs approved** by the U.S. Food and Drug Administration **from 2010 to 2019** (57).

Cancer Development: Generating Knowledge

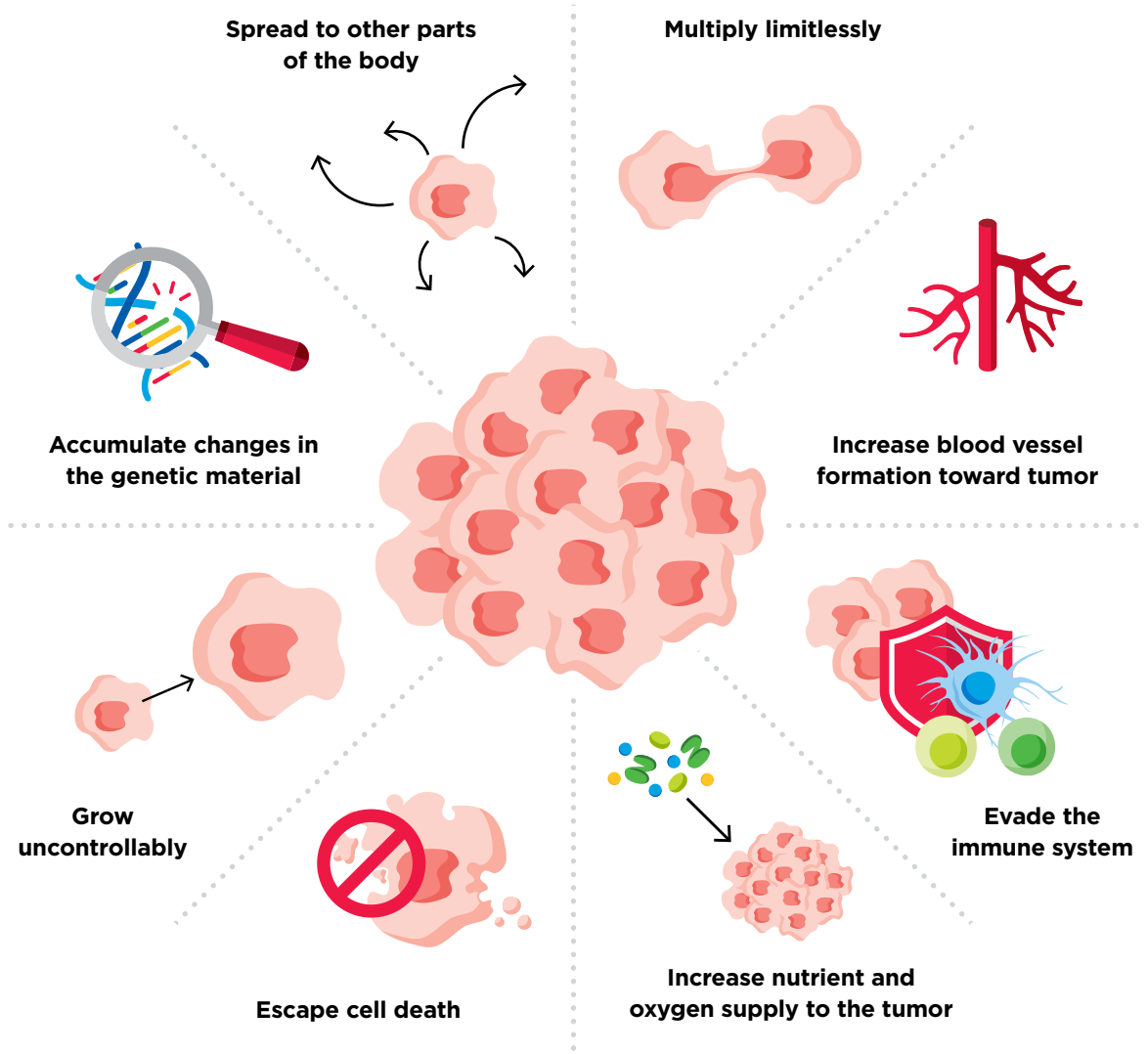
Much of the current knowledge of how cancer develops comes from basic research. Sometimes called "pure" or "fundamental" science, basic research helps researchers understand living systems and life processes. This knowledge is essential to develop better ways to predict, prevent, detect, diagnose, and treat disease.

Knowledge gained from basic research provides the foundation for new advances in clinical care and refines existing practices. Recognizing the critical role of basic research in improving the overall health for all individuals, NIH has spent more than 50 percent of its budget on basic research every year over the past two decades (64).

Basic research is a fundamental component of medical research (see **Figure 4**, p. 27). Scientists working across the spectrum of medical research seek to address biological and/or clinical significance of a new discovery through experiments in a wide range of models that mimic healthy and diseased conditions.

FIGURE 3

Hallmarks of Cancer Cells



During the course of cancer development, abnormal or damaged cells acquire so-called "hallmarks" or characteristics that distinguish cancer cells from normal cells. Some of the hallmarks of cancer cells include the ability of cancer cells to divide limitlessly, grow uncontrollably, escape cell death, spread to other tissues in the body, evade destruction by the immune system, and increase nutrients and oxygen supply to tumors.

Adapted from (62).

Findings from these experiments can identify new targets for drug development; develop the technologies needed to generate drugs that are selective for cancer cells or cancer targets; inform approaches for preventive intervention; determine new strategies for early detection; or uncover predictive or prognostic biomarkers, each of which has the potential to improve public health.

Once researchers identify a potential therapeutic target, potential therapeutic agents can be generated and pursued in translational and clinical studies designed to carefully test candidate therapeutics against the target and determine the appropriate dosage, dosing schedules, and toxicities. These preclinical studies help determine the most promising candidates, which are then tested in clinical trials (see **Sidebar 27**, p. 71).

Progress made against cancer in recent decades is a direct result of years-long cross disciplinary collaborations among stakeholders working throughout the medical research cycle (see **Sidebar 1**, p. 13 and **Figure 4**, p. 27).

SIDEBAR 5

How Are Cancers and Tumors Characterized?

Cancer is a collection of diseases characterized by the uncontrolled proliferation of cells. Depending upon the type and purpose of the reporting, a combination of two or more classification and staging approaches is used to identify and describe the type of cancer a person has:

BY SITE OF ORIGIN

Classifies cancers based on the organ in which cancer originated, e.g., breast cancer, or lung cancer.

BY TISSUE TYPE

Classifies cancers based on the type of tissue in which cancer originated.

Carcinoma
Begins in the skin or in tissues that line or cover internal organs.

Sarcoma
Begins in bone or in the soft tissues of the body, such as fat or muscle.

Myeloma
Begins in plasma cells, a type of white blood cell.

Leukemia
Begins in blood-forming tissue, such as the bone marrow.

Lymphoma
Begins in cells of the immune system.

BY GRADE

Classifies cancers based on how tumor cells appear when examined under a microscope. If cells look more normal, a tumor might be called well differentiated in the pathology report. If cells look less normal, a tumor might be called poorly differentiated or undifferentiated and is considered more aggressive.

GRADE X Undetermined grade
When a grade cannot be assessed.

GRADE 1 Low grade
When cells are well differentiated.

GRADE 2 Intermediate grade
When cells are moderately differentiated.

GRADE 3 High grade
When cells are poorly differentiated.

GRADE 4 High grade
When cells are undifferentiated.

BY SPREAD

Classifies cancers based on the extent to which cancer has spread in the body. This approach to describe cancer is called the TNM staging system (where T refers to the primary tumor; N refers to the regional lymph node—a tissue in the lymphatic system (see **The Lymphatic System**, p. 33); and M stands for metastasis—when cancer has spread to parts of the body that are distant from the primary site of origin.

In the TNM staging system, clinicians consider the size of the tumor (larger size is typically considered a more aggressive tumor), and whether the cancer has spread from where it started to nearby lymph nodes (higher number of lymph node containing cancer is typically considered a more aggressive cancer), or other parts of the body (metastasis). A simplified description of cancer stages using this approach is described below:

Precancerous stage
A condition that may become cancer in the future if untreated.

Stage I
Cancer that is localized to the tissue of origin.

Stage II
Cancer that has spread to nearby tissues.

Stage III
Cancer that has spread to nearby lymph nodes or other tissues to a higher extent than Stage II.

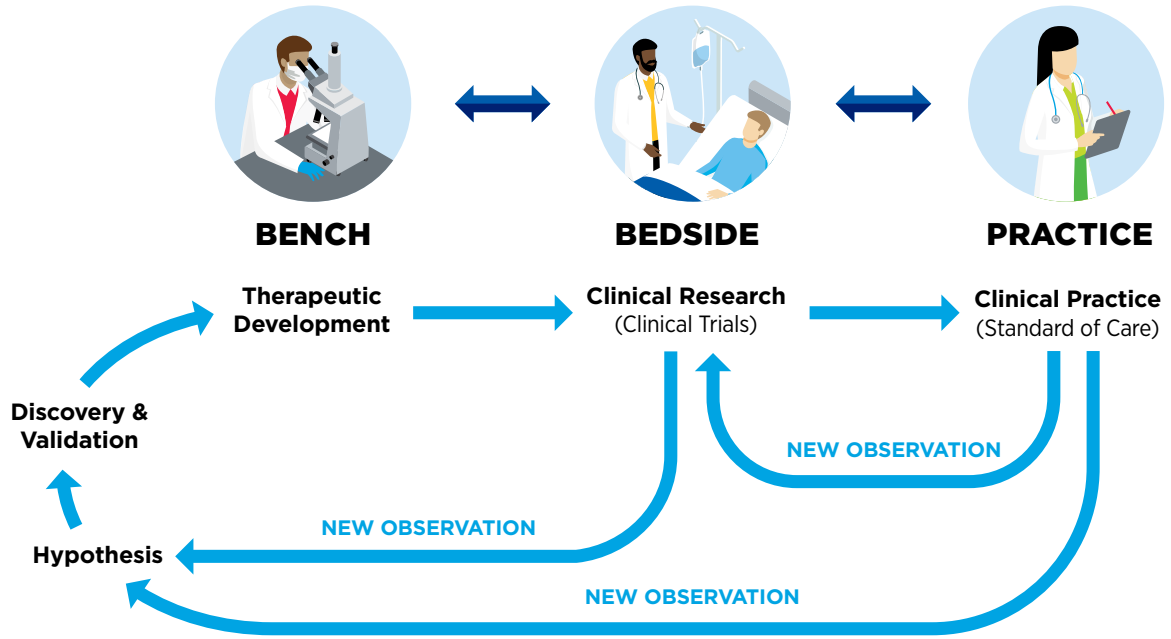
Stage IV
Cancer that has spread to distant lymph nodes or other distant tissues.

It is important to note that characterization of cancers, as well as their treatment, increasingly includes biological and molecular properties of cancer, thanks to research-driven knowledge of the genetic and epigenetic makeup of cancer. For example, breast cancer is further characterized by the presence or absence of estrogen, progesterone, and HER2 receptors.

Developed from (63).

FIGURE 4

The Research Cycle Advancing the Frontiers of Cancer Science and Medicine



The medical research cycle is a self-driven process with a primary goal to save and improve lives. Findings from any type of basic research can lead to new questions and generate new hypotheses relevant to the practice of medicine. The discovery phase of the medical research cycle uncovers new targets for developing better and more effective treatments. Potential therapeutics can be designed and first tested in preclinical models mimicking normal and disease conditions to identify any harmful effects and determine initial dosing. The safety and efficacy of potential therapeutics are then tested in clinical trials. If an agent is safe and effective, it is approved for use in the clinic by the U.S. Food and Drug Administration (FDA). Importantly, observations made during the routine use of a new therapeutic can further improve its use or inform the development of others like it. Even for therapeutics that are not approved by FDA, observations from preclinical and/or clinical testing can spur future research efforts.

In addition to fueling the development of safer and more effective therapeutics, scientific knowledge gathered through basic, translational, and clinical research, as well as from population science, informs evidence-based guidelines for cancer screening, preventive interventions, and other public health policies and regulations.

Adapted from (4).

Basic Research: Vital for Making Progress Against Cancer

Basic research, together with translational and clinical studies and population sciences, has played a pivotal role in reducing the burden of cancer in the United States. Discoveries stemming from decades of basic research have provided the foundational knowledge, which has led to a 33 percent reduction in the overall cancer mortality rate over the last three decades (see **Sidebar 6**, p. 28). One example of how basic research contributes to progress against cancer is the development of small molecule inhibitors of Kirsten rat sarcoma viral oncogene homologue (KRAS), a protein that is essential for the growth and survival of normal cells and is altered in many cancers.

Several teams of basic researchers simultaneously identified the human *KRAS* gene in 1982 (65). Subsequent discoveries linked KRAS activity with growth and survival of normal cells and identified alterations in the gene that were associated with human cancer (65). More recent studies have established that the *KRAS* gene is frequently mutated (see **Sidebar 7**, p. 30) in several cancer types, including cancers of the pancreas, lungs, and colon and rectum (66). Up until 2021, KRAS was considered an undruggable protein, and patients with cancer harboring KRAS mutations had limited treatment options.

Thanks to the research-driven technological innovations, advances in synthetic chemistry and structural biology, and a deeper understanding of the genetic alterations in lung cancer, researchers

SIDEBAR 6

Basic Research Driving Clinical Advances Against Cancer

BASIC RESEARCH DISCOVERY	CLINICAL BREAKTHROUGH	CURRENT STATUS
1980s The human *HER2* gene is identified and sequenced.	**1998** FDA approves trastuzumab (Herceptin), an antibody targeting HER2, to treat patients with HER2-positive **metastatic breast cancer**.	**July 2023** So far, trastuzumab, alone, in combination with other drugs or as antibody-drug conjugates, has been approved by FDA to treat patients with certain types of **breast, gastric, lung, and colorectal cancers**.
1980s BCR-ABL protein, a product of the Philadelphia chromosome, is identified as a possible cause of **chronic myelogenous leukemia (CML)**.	**2001** FDA approves imatinib (Gleevec), a targeted therapeutic against BCR-ABL, for treatment of patients with **CML**.	**July 2023** So far, six therapeutics targeting BCR-ABL have been approved by FDA to treat **CML**.
1980s The human *RET* gene is identified and its rearrangements in **thyroid cancer** are documented.	**2020** FDA approves selpercatinib (Retevmo), a molecularly targeted therapeutic that inhibits RET activity, to treat **thyroid cancer**.	**July 2023** So far, two RET-targeted therapies have been approved by FDA for treatment of **lung and thyroid cancer**, as well as **any solid tumor based on a certain biomarker**.
1980s The human *PARP-1* gene is identified and its role in DNA repair is discovered. **1990s** The human *BRCA1* and *BRCA2* genes are identified and their role in DNA repair is discovered.	**2014** FDA approves olaparib (Lynparza), a molecularly targeted therapeutic that inhibits PARP activity, to treat women with **advanced ovarian cancer** who inherited mutations in *BRCA1/2* genes.	**July 2023** So far, four PARP-targeted therapeutics have been approved by FDA for treatment of **breast, ovarian, pancreatic, and prostate cancers**.
1980s The human NTRK is identified as an oncogene and its rearrangements in **colorectal and thyroid cancers** are documented.	**2018** FDA approves larotrectinib (Vitrakvi), a molecularly targeted therapeutic that inhibits NTRK activity, to treat children and adults whose tumors are carrying NTRK rearrangements.	**July 2023** So far, two NTRK-targeted therapies have been approved by FDA for treatment of **any solid tumor based on NTRK rearrangements**.

have developed several small molecular inhibitors that successfully inhibit the activity of the mutant KRAS in patients with NSCLC. One of the compounds, sotorasib (Lumakras), was approved by FDA in May 2021 (4), and a second compound, adagrasib (Krazati), was approved in December 2022 (see **Expanding Treatment Options for Patients with Lung Cancer**, p. 83).

Basic research provides the foundational knowledge about what triggers cancer development; how cancer evades the body's defenses; and how cancer spreads within the body, among other aspects of cancer biology (see **Cancer Development: Interpreting Knowledge**, p. 29). Basic research is also fueling the development of molecules that can help visualize cancer cells better, deliver drugs to tumors more precisely, and kill cancer cells more selectively and effectively. Collectively, basic research-driven advances are contributing to progress against cancer that is saving lives and improving health outcomes for countless patients.

Cancer Development: Interpreting Knowledge

At a fundamental level, cancer is a genetic disease that is caused by changes in genes that control vital functions, such as cell multiplication and cell growth (see **Sidebar 7**, p. 30). However, transformation of normal cells into cancer cells, accumulation of cancer cells to form tumors, and spread of tumors to distant sites in the body are all complex, multistep processes that are influenced by alterations inside the cell as well as changes outside the cell.

Changes That Contribute to Cancer Initiation

Cellular functions are dictated by instructions that are encoded in deoxyribonucleic acid (DNA), a complex molecule that constitutes the genetic material of cells. Four unique molecules or bases, designated A, T, C, and G, make up a DNA strand, and two DNA strands are then paired together to form a double helix. The entirety of a person's DNA is called the genome.

Inside the nucleus of human cells, the DNA double helix is wrapped around bead-like structures called nucleosomes, which are composed of proteins called histones. The packaged DNA is further compacted in multiple layers, making up structures we know as chromosomes. Nearly all human cells have 46 chromosomes.

Genes are pieces of DNA and there are hundreds to thousands of genes contained in each chromosome. Genes carry instructions or messages for making proteins, which are functional units of the cell. The cell uses a complex process, called transcription, to copy the message embedded in a gene to make another type of molecule called messenger ribonucleic acid (mRNA). The information in mRNA is subsequently "translated" into proteins. Cellular needs influence how much mRNA or protein will be produced.

The following section describes the types of changes within a cell that impact cancer development.

Genetic Alterations

Alterations in the DNA sequence, referred to as mutations, can disrupt or modify normal protein function and are among the hallmarks of cancer cells. Gene alterations can change the sequence or amount of mRNA and the resulting proteins that are produced, which in turn can contribute to cancer development (see **Sidebar 7**, p. 30). Genetic alterations can be inherited (called germline mutations) or acquired during a person's lifetime (called somatic mutations). In about 10 percent of cancer cases, the mutations are inherited.

Germline mutations occur in a body's reproductive cells (egg or sperm) that are passed on from parents to children and become incorporated into the DNA of every cell in the body of the offspring. These types of mutations can increase their risk of developing cancer, although not all germline mutations contribute to cancer development. Inherited genetic alterations that play a role in cancer development are among the pathogenic germline mutations (see **Figure 5**, p. 31).

We are making great strides in understanding germline pathogenic mutations, thanks to advances in research and technology. As one example, a recent study utilizing cutting edge DNA sequencing found that 13 percent of patients with endometrial cancer had germline pathogenic mutations, and 63 percent of these mutations occurred in genes that are known to drive cancer development (69). These findings can help researchers identify new ways to test individuals and their family members for risk of developing endometrial cancer, as well as devise new strategies for minimizing the possibility of developing cancer.

Somatic or acquired mutations occur over an individual's lifetime due to errors arising during normal cell divisions or because of environmental exposures, lifestyle factors, and/or health conditions. Research has revealed that tumors originating from different sites, as well as different tumor masses originating from a primary tumor within a person, contain different somatic mutations. For example, two recent studies evaluated metastatic tumors from different patients and from different sites within each patient to understand how metastatic lung cancer grows and spreads inside the body. Findings from these studies showed that genetic features of metastatic lung tumors from separate sites differed greatly within a patient and across patients and that these differences determined when and how the cancer would recur (70,71).

SIDEBAR 7

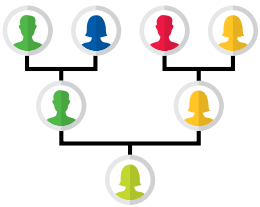
What Are Genetic Alterations?

Genetic alterations are changes in the DNA sequence. While not all genetic alterations cause cancer, many can result in downstream changes in the sequence or amount of mRNA and/or proteins produced, some of which can drive or contribute to cancer development. Genetic alterations are one of the hallmarks of cancer cells.

HOW ARE GENETIC ALTERATIONS ACQUIRED?

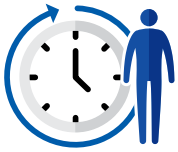
Cells can acquire genetic alterations in a number of ways, including:

By inheritance from parents



During a person's lifetime from:

- Certain viral infections
- Smoking
- Extended exposure to UV radiation
- Exposure to mutagens or other cancer-causing chemicals
- Errors made during cell division



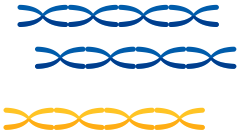
WHAT TYPES OF GENETIC ALTERATIONS CONTRIBUTE TO CANCER DEVELOPMENT?

Single base changes

Refers to deletion, insertion, or substitution of a single base (designated A, T, G, C) in DNA that can result in new proteins, altered versions of normal proteins, loss of protein function, or changed amount of the protein produced.

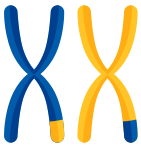
Gene amplification

Reflects extra copies of genes in the genome, causing higher quantities of certain proteins that can enhance cell survival and growth.



Structural variations

Arise when two separate genes or pieces of chromosomes join to produce a new protein or different amount of protein.



Deletions

Indicate loss of DNA, which can result in loss of genes necessary to regulate the processes that control normal cell growth, multiplication, and life span.

In addition, recent findings have shown that many other types of changes to a cell's DNA, such as the presence of extrachromosomal DNA (ecDNA)—particles of viral or self-DNA existing outside the genome—in human cells, also contribute to cancer development (see **New Frontiers in Cancer Research**, p. 143).

It is important to note that not all genetic alterations contribute to cancer.

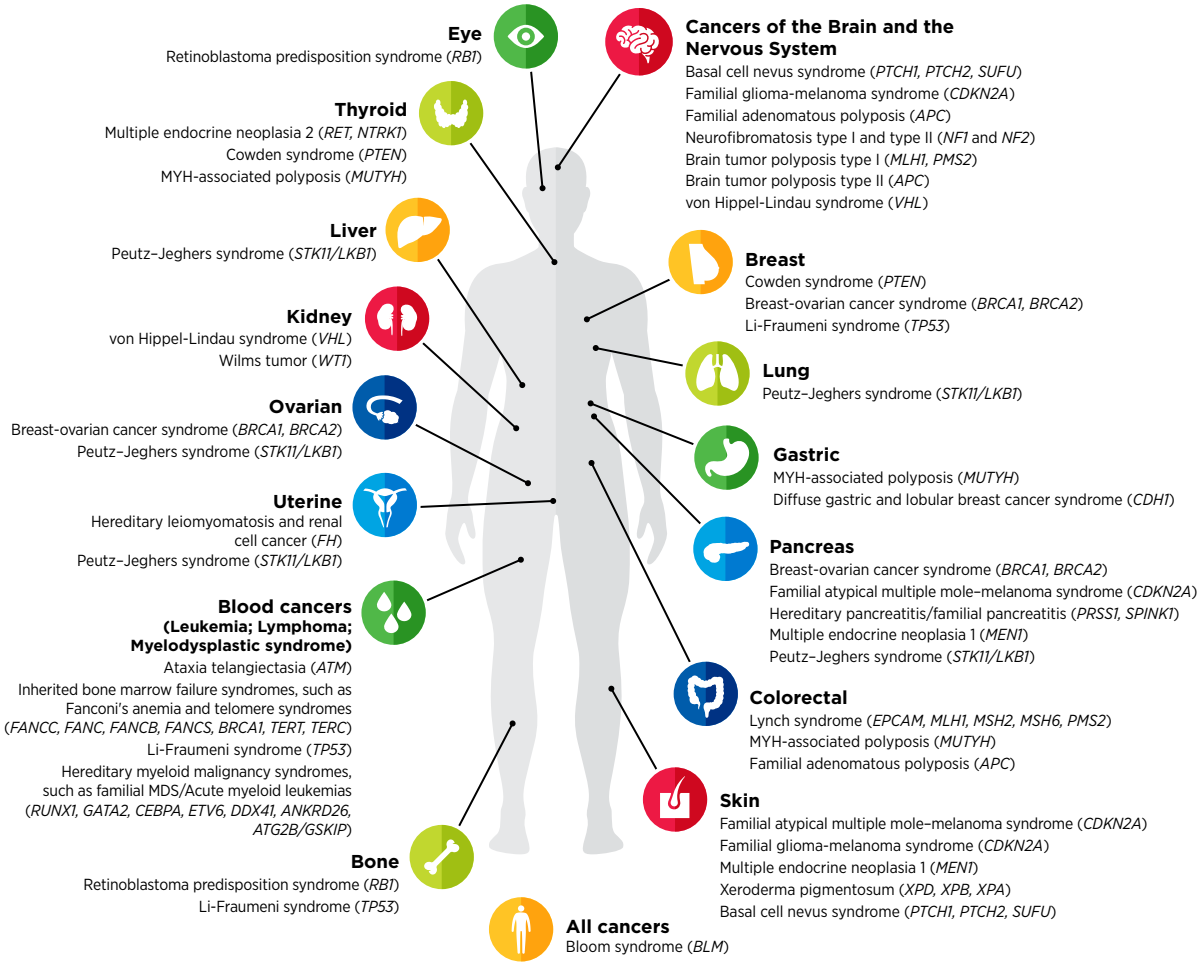
Adapted from (67,68).

Clonal hematopoiesis is a condition in which **somatic mutations associated with blood cancers** are **detected when DNA from blood cells of healthy individuals** is sequenced for other clinical reasons. Clonal hematopoiesis **increases with age** and is associated with an **increased risk of developing blood cancer** (72).

Researchers are leveraging knowledge of genetic alterations in cancer to develop approaches that are driven by artificial intelligence for establishing comprehensive maps of somatic mutations across different cancer types. In a recent study, researchers developed a deep learning model that identified known and previously unknown somatic mutations as drivers of cancer development across 37 types of cancers (73). Characterizing cancers at a molecular level based on the types of genetic alterations, as well as understanding how genetic mutations contribute to cancer, has led to the development and FDA approval of many molecularly targeted therapies (74). Recent research efforts are focused on understanding how germline and somatic mutations work together to cause cancer, and whether this knowledge can be applied to find new ways to test for and

FIGURE 5

Inherited Cancer Risk



Depicted here are selected cancer types that are associated with inherited cancer syndromes. Also shown in parentheses are the genes, mutations in which are linked with various inherited cancer syndromes that predispose individuals to the shown cancer types.

Developed from (1).

treat cancer, monitor responses to therapy and/or determine an individual's risk of developing cancer over their lifetime (75-77).

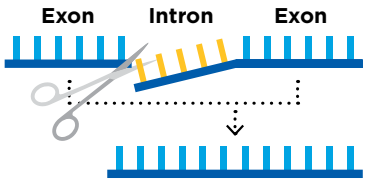
RNA Variations

Most human genes contain information for making proteins in fragments of DNA, called exons. Exons are interspersed by DNA sequences, called introns, that do not contain information necessary to make a functional protein. When a gene is transcribed into mRNA, the initial mRNA molecule contains a copy of both exons and introns. An intricate "cut and paste" process, called splicing, removes introns and joins exons together to produce an mRNA molecule that is subsequently translated into a functional protein by the cellular machinery.

RNA splicing plays a pivotal role in normal cellular functions. In cancer cells, changes in proteins necessary for splicing can produce aberrant mRNA molecules, which subsequently make abnormal proteins that can fuel cancer development, lead to treatment resistance, and alter immune cell function (78). Ongoing research is focused on understanding how cancer-related changes in RNA splicing can be leveraged for therapeutic purposes (79).

Researchers are also using transcriptomics—the study of all RNA molecules in a cell—to establish comprehensive patterns of the types and levels of RNA, or transcriptomes, present in healthy tissues versus tumors. Knowledge gleaned from such studies helps researchers understand how different types of RNA may contribute to cancer development. Technological breakthroughs

A recent analysis of 395 samples from patients with pancreatic cancer found that **RBFOX2, a protein critical for RNA splicing**, plays a **crucial role in preventing metastatic transformation** of early-stage pancreatic cancer, and **may serve as a therapeutic target in pancreatic cancer** (80).



in RNA sequencing with higher precision and accuracy have further allowed researchers to determine transcriptomes of single cells. Such analyses are unveiling previously undiscovered mechanisms that contribute to cancer development (81), tumor heterogeneity (see **Tumor Heterogeneity**, p. 34), and treatment resistance (82).

Protein Modifications

Proteins are vital for normal cellular functions. The human proteome—the complete set of proteins made by humans—contains about 20,000 unique proteins. After being produced from mRNA, proteins can undergo additional modifications, providing great versatility and variability in their functions to meet cellular needs. Examining the proteome of cancer cells can unveil additional information about how cancer develops. For example, a recent study evaluated proteomes of nearly 1,000 cancer cell lines—tumor-derived cells that keep dividing and growing under certain conditions in the laboratory and are commonly used in medical research to understand molecular underpinnings of cancer development. Researchers identified common and unique cancer-related changes in levels of many proteins that were not detected at DNA or RNA levels (83).

Modifications of proteins, also called posttranslational modifications (PTMs), are often necessary for normal cellular functions, such as responding to signals from outside the cell (84). Changes in normal PTMs of proteins can contribute to cancer (85). Identifying cancer-related PTM(s) has been central to developing effective anticancer therapeutics. Research has shown that many enzymes—specialized proteins that speed up chemical reactions in the body—that mediate PTMs exhibit altered function in cancer cells and are an attractive target for therapeutic development. This knowledge has led to the development and FDA approval of numerous molecularly targeted therapies that function by inhibiting the activity of such enzymes (74), thus expanding treatment options available to patients with cancer.

Epigenetic Changes

Epigenetic changes alter the structure of DNA without changing the DNA sequence. Epigenetic alterations occur when chemical marks are added to or removed from DNA, or when histone proteins undergo PTMs. Epigenetic changes may be acquired with age and/or exposure to environmental factors (e.g., air pollution) or behavioral factors (e.g., smoking) and psychosocial stressors (e.g., systemic racism), and may affect a person's risk of cancer as well as be passed from parent to child.

Epigenetic modifications regulate how and when genes are turned on or off. Specialized proteins add or remove unique epigenetic modifications to and from DNA and histones (86). In contrast to genetic mutations, most epigenetic changes are reversible.

Cancer cells exhibit an altered epigenome—the complete set of all of the epigenetic changes in a cell. Because epigenetic changes are attractive targets for drug development, an area of active research is understanding how changes to the epigenome contribute to cancer development and how such changes can be targeted. Research over the years has led to development and approval of several anticancer therapeutics that function by modifying the cancer epigenome (87).

Researchers are also leveraging the knowledge of the epigenome to categorize different types of cancer at a molecular level. For example, research has shown that mutations in proteins that add or remove epigenetic modifications are characteristics of glioma, a devastating type of brain cancer in children and adults (88). These findings can help identify new therapeutic targets in glioma and can accelerate the development of new drugs to treat this aggressive form of cancer.

Systems That Enable Cancer Progression

A hallmark of cancer is the ability of tumor cells to break away from the primary tissue and travel to other parts of the body. Systems that enable cancer to spread from the primary tissue to other organs of the body include the blood system, the lymphatic system, and the immune system (see **Sidebar 8**, p. 33).

The Blood System

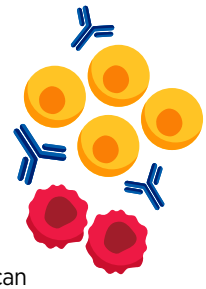
The formation of new blood vessels, called angiogenesis, is a normal and essential process that occurs throughout life and is controlled by chemical signals in the body. The ability to promote angiogenesis toward and within a tumor is a hallmark of cancer. Tumor angiogenesis supplies high levels of oxygen and nutrients that are required to fuel rapid tumor growth.

SIDEBAR 8

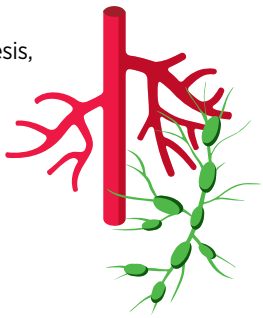
Cancer Growth: Local and Systemic Influences

Solid tumors are much more complex than an isolated mass of proliferating cancer cells. Cancer development is strongly influenced by interactions between cancer cells and numerous factors in their environment. Among the components of the tumor microenvironment are the following:

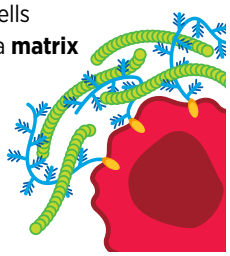
Immune cells can identify and eliminate cancer cells, although in many cases cancer cells acquire characteristics that help them evade the immune system, permitting the formation and progression of a tumor. However, in some situations of chronic inflammation, the immune system can promote cancer initiation and progression.



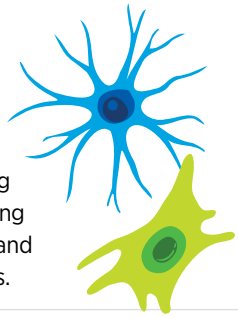
Cancer cells can stimulate a process called tumor angiogenesis, the growth of **blood and lymphatic vessel networks**, which supply the cancer cells with the nutrients and oxygen required for rapid growth and survival and provide a route for cancer cell escape to distant sites (metastasis).



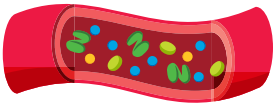
Chemical signals from cancer cells contribute to the formation of a **matrix of proteins** that surrounds the tumor and provides structural and biochemical support. This ultimately regulates proliferation of cancer cells, supports tumor growth, and eventually aids in tumor metastasis.



Other **tissue-specific** tumor-associated **cells**, such as pericytes, fibroblasts, and astrocytes, can support tumor growth through various mechanisms including stimulating tumor cell multiplication, triggering formation of new blood vessels, and enhancing survival of cancer cells.



Systemic factors in the circulation, such as growth factors (e.g., hormones) and nutrients, influence the development and growth of cancer.



Adapted from (4).

Therefore, drugs that block angiogenesis can restrict the ability of a tumor to grow, divide, and metastasize.

Several proteins play pivotal roles in angiogenesis. One such protein is vascular endothelial growth factor (VEGF), which functions in concert with its binding partner, called the VEGF receptor. There are several forms of both proteins, and both proteins are essential for the growth of cells that line the inside of blood vessels. Decades of research have shown that cancer cells can produce and release high levels of VEGF, thus directing the formation of new blood vessels (89).

Advances in cancer therapeutics over the past two decades have led to the development of drugs that inhibit the function of VEGF and the VEGF receptor, thus blocking a tumor's efforts to increase the supply of oxygen and nutrients. In 2004, FDA approved bevacizumab (Avastin), the first anti-angiogenic drug targeting a form of VEGF. Since then, FDA has approved 11 different anticancer therapeutics targeting several forms of VEGF or VEGF receptors, or other proteins that promote angiogenesis, to treat 13 different cancer types (4).

The Lymphatic System

The lymphatics are an extensive system of vessels, called lymph vessels or lymphatic vessels, and small bean-shaped structures, called lymph nodes. Other organs such as the spleen, thymus, tonsils, and adenoids are also part of the lymphatic system. The lymphatic system runs throughout the body and is an essential component of the immune system. Key functions of the lymphatic system include maintaining total body fluid levels, removing cellular waste from tissues, detecting pathogens, absorbing fats, and producing immune cells and antibodies in the lymph nodes.

When cancer cells break away from a tumor, they can travel to other parts of the body through the blood or the lymphatic system. If cancer cells spread through the lymphatic system, they may accumulate in one or more of the nearest lymph nodes. The presence of cancer cells in lymph nodes is used to determine the stage and/or the extent of cancer (see **Sidebar 5**, p. 26).

Tumor cells can enter the lymphatic system in several ways, including adopting mechanical changes that facilitate cancer cell entry into the lymphatic system, and releasing certain molecules that help cancer cells move toward the lymphatic vessels (90). Once inside the lymphatic system, cancer cells acquire additional properties that make them more aggressive and facilitate their spread to other parts of the body (91).

Ongoing research is focused on leveraging contributions of the lymphatic system in cancer growth and spread, including targeted delivery of anticancer therapy to lymph nodes as well as the development of drugs that block the migration of cancer cells toward lymphatic vessels (90).

The Immune System

The immune system is a complex network of cells, tissues, organs, and the substances they make that help the body fight infections and other diseases, including cancer (see **Sidebar 8**, p. 33, and **Sidebar 38**, p. 100). The immune system actively detects and eliminates abnormal or damaged cells from the body. However, because of the heterogeneous nature of the changes cancer cells acquire over time, some cancer cells obtain properties that help them evade the immune system. The properties of cancer cells that facilitate evasion from the immune system are one of the hallmarks of cancer.

Extensive research over the last three decades has revealed some of the ways cancer cells evade the immune system (92). These include disruption of the cellular machinery that helps immune cells recognize damaged or abnormal cells; increasing levels of proteins in tumor cells that function as brakes on the immune system; and release of molecules that prevent the immune cells from becoming fully functional (93). Research has also shown that certain immune cells present in the tumor microenvironment (see **Tumor Microenvironment**, p. 35) can promote tumor growth (94). This issue of the AACR Cancer Progress Report includes a spotlight on advances in immunotherapy that highlights the tremendous progress that has been made in recent decades to harness the potential of the immune system to treat cancer (see **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99).

Processes That Promote Cancer Growth and Metastasis

Cancer metastasis refers to the spread of cancer cells from the tissue where they first originated to another part of the body. During metastasis, cancer cells break away from the original (primary) tumor, travel through the blood or lymph system, and form a new tumor in other organs or tissues of the body. Although the new, metastatic tumor acquires many additional alterations during the course of cancer development, it remains the same type of cancer as the primary tumor. For example, if prostate cancer spreads to the bone, the cancer cells in the bone are prostate cancer cells, not bone cancer cells.

Patients with metastatic cancer have considerably lower 5-year survival rates than those with localized cancer (28). More than 90 percent of cancer-related deaths result from metastatic disease (95). Furthermore, chances of a cure are limited in patients with metastatic cancer, and thus researchers are continually uncovering additional complex processes that facilitate cancer metastasis.

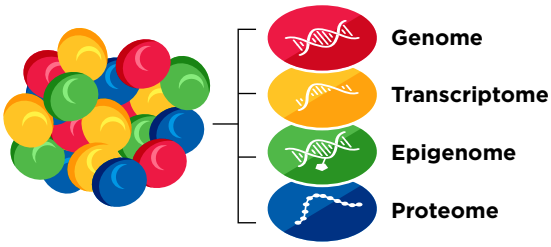
Tumor Heterogeneity

During the course of disease, as cancer cells divide, they continue to acquire new alterations in their genomes, epigenomes, transcriptomes, and proteomes in various combinations and become more heterogeneous. Researchers use the term 'tumor heterogeneity' to describe the differences between cancer cells within a single tumor, the differences between tumors of the same type in different patients, or the differences between a primary (original) tumor and the metastatic tumor.

Tumor heterogeneity plays a crucial role in cancer development and influences how cancer spreads, and how it responds to treatment. The heterogeneity of cancer cells in the primary tumor enables some tumor cells to acquire properties that facilitate their spread to other parts of the body. Tumor heterogeneity is also one of the major reasons why certain patients with cancer are resistant to treatments (96) (see **Sidebar 35**, p. 87).

SINGLE-CELL SEQUENCING

Sequencing of genomes, transcriptomes, epigenomes, and proteomes of individual cells **allows researchers to understand the cellular and molecular features of cancer** at the level of single cells, and **helps discover aspects of cancer development**, such as tumor heterogeneity, that may not be apparent from the averaged data obtained from sequencing all or part of the tumor (97).



Technological advances in sequencing and molecular imaging are enabling researchers to decode the heterogeneous nature of tumors at the single cell level. As one example, an analysis of transcriptomes of 1,163 tumor samples across 24 cancer types identified 41 different types of mRNA expression patterns that were common among the cancer types tested. Although there were common genes involved in cancer development across different cancer types, researchers found that individual cells within a tumor were highly heterogeneous in terms of the types of mutations they carried (98), which can yield both underlying resistance to therapy as well as distinct vulnerabilities. Understanding and therapeutically targeting tumor heterogeneity is the next frontier in cancer science and medicine.

Epithelial-to-mesenchymal Transition

Epithelial cells are the cells that tightly connect with each other to form the covering of all body surfaces, line body cavities and hollow organs, and are the major tissue in glands. Roughly 90 percent of cancers develop in epithelial cells (99).

Cancers that develop in epithelial cells acquire properties of another type of cells, called mesenchymal cells, which form the connective tissue, blood vessels, and lymphatic tissue, and have the ability to migrate within the body. Cancer cells acquire the mesenchymal characteristic of moving within the body by hijacking pathways fundamental for epithelial-to-mesenchymal cell transition, or EMT, which is an essential process for the formation of organs during normal embryonic development (100). Hijacking of EMT pathways by cancer cells is one of the hallmarks of cancer.

Research has established that EMT is regulated by several proteins that promote cancer cell division, survival, and mobility, and enable metastasis (101,102). Recent studies have found that EMT also plays a critical role in the ability of cancer cells to evade the immune system (103). Ongoing research is exploring whether therapeutically targeting EMT could improve clinical outcomes.

Tumor Microenvironment

Cancer cells interact with and modify surrounding cells and tissues to sustain their ability to multiply unchecked and accumulate in the primary tissue of origin. The cells, molecules, and blood vessels that surround and sustain cancer cells collectively form the tumor microenvironment.

The tumor microenvironment can affect how a tumor grows and spreads, and cancer cells can reciprocally influence the tumor microenvironment (see **Sidebar 8**, p. 33). For instance, cancer cells can release molecules that shape their surrounding environment to provide them with nutrients, oxygen, and a supportive structure. The tumor microenvironment, in turn, can adapt to make it difficult for the immune cells or anticancer drugs to reach and eliminate tumor cells (104,105).

The vital role of tumor microenvironment in cancer initiation, progression, and metastasis has made it a key target for therapeutic development. For example, researchers are working to modify certain types of immune cells such that these cells can infiltrate the tumor microenvironment and destroy cancer cells (106) (see **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99). Blocking the supply of oxygen and nutrients with anticancer therapeutics that inhibit tumor angiogenesis has also shown great promise in therapeutically targeting the tumor microenvironment (106).

Cancer Development: Integrating Knowledge

We are making remarkable strides toward understanding how cancer develops, grows, and spreads, thanks to contributions of countless researchers across the spectrum of cancer science and medicine. Knowledge gleaned from medical research has already enabled the development of effective anticancer therapies that offer hope to many patients with cancer (see **Advancing the Frontiers of Cancer Science and Medicine**, p. 68). In parallel, technological advances in our ability to investigate characteristics of cancer cells at single cell and single molecule levels are providing an in-depth knowledge of the complexities of cancer.

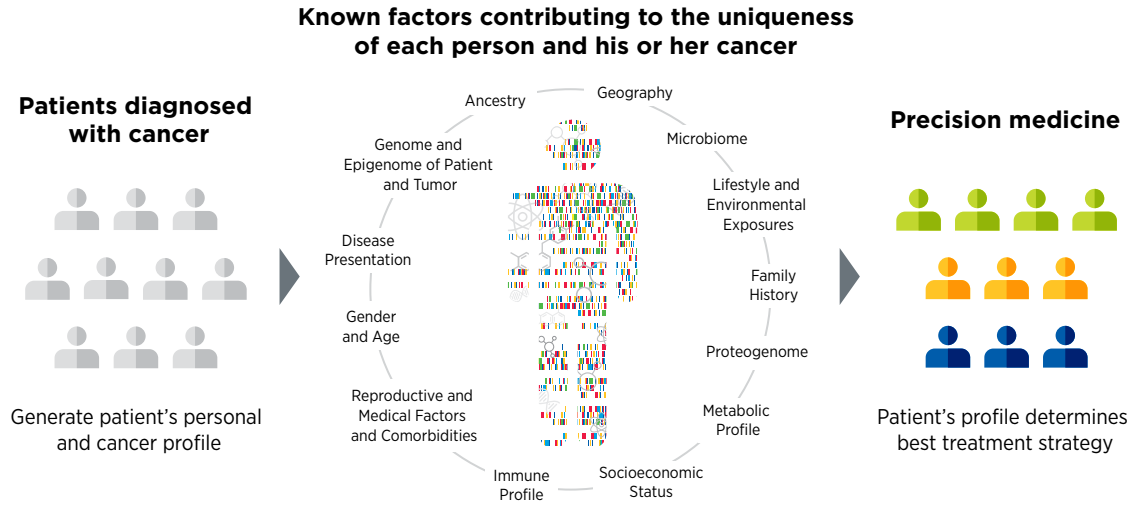
One of the most important insights gleaned from this knowledge is that each patient's cancer is unique at the molecular level. Together, these insights have provided the basis for precision medicine, also called personalized medicine. Precision medicine is broadly defined as treating patients based on characteristics that distinguish them from other individuals with the same disease (see **Figure 6**, p. 36).

In cancer, precision medicine means using specific information about a patient's tumor, such as the genome sequence of cancer cells, to help make a diagnosis, plan treatment, evaluate whether treatment is working, and/or predict prognosis. In recent years, FDA has approved an increasing number of anticancer therapeutics that are developed on the basis of genomic characteristics, and many molecularly targeted drugs are being used to treat cancers that originate from different organs but share similar genomic characteristics (see **Advancing the Frontiers of Cancer Science and Medicine**, p. 68) (107,108).

The next frontier of precision medicine is to integrate our ever-growing knowledge of the genome, epigenome, proteome, transcriptome, microbiome (see **Targeting the Microbiome in Cancer Treatment**, p. 150), immune system and other

FIGURE 6

Precision Medicine



Precision medicine, also called personalized medicine, is broadly defined as treating patients based on characteristics that distinguish them from other individuals with the same disease. As shown in the figure, the factors that contribute to the uniqueness of a patient and his or her cancer include, but are not limited to, the person's and tumor's genome, epigenome, transcriptome, proteome, microbiome, metabolome, the immune characteristics of the person and of cancer, disease presentation, gender, ancestry, exposures, lifestyle, and comorbidities. Currently, genomics is the predominant factor influencing precision medicine, but as we learn more about the additional factors, such as epigenomics, proteogenomics, metabolomics and tumor immune characteristics, we have begun to integrate this knowledge to further refine the personalized approach to cancer treatment. Although genomic and epigenomic profiling of a patient and of his or her tumor is becoming a routine in the clinic, it is important to note that the cost effectiveness of comprehensive profiling that includes all the other characteristics shown in the figure still needs to be evaluated, alongside ongoing efforts to define which and to what extent profiling improves outcomes for individuals.

information about a patient to create a treatment that is tailored to his or her tumor. In fact, researchers are already integrating multiple molecular aspects of a patient's tumor to determine characteristics that can improve cancer diagnosis; to identify drug targets that can treat cancer precisely; and to establish features that can predict treatment responses and outcomes accurately (111).

In the United States, NCI is playing a vital role in supporting research in precision cancer medicine (see **Sidebar 9**, p. 37). For example, results from NCI's initial investments in the Clinical Proteomic Tumor Analysis Consortium (CPTAC) are laying the foundation for the next horizon in precision medicine, called proteogenomics (112).

Proteogenomics is the study of how information about the genome of a cancer cell relates to the proteins made by that cell. This includes understanding how genes control when proteins are produced and what changes occur to proteins after they are made that may switch them on and off. Proteogenomics research can help us learn more about which proteins are involved in certain diseases, such as cancer, and may also be used to help develop new drugs that block these proteins.

In a recent study, researchers performed proteogenomic profiling of tumor samples from patients with early esophageal cancer—an aggressive type of cancer, whose underlying biology is not well known. Findings of the study uncovered six distinct molecular signatures that may be related to the development of esophageal cancer, and identified a protein involved in energy production by cells as a novel drug target (113). Several recent studies have carried out similar analyses for other diseases such as gastric cancer (114), glioma (115), leukemia (116), breast cancer (117), and bladder cancer (118), among others. Researchers can now use this information to further refine approaches to diagnose and treat these cancers.

Precision medicine holds immense promise to deliver better outcomes with reduced toxicity for patients with cancer. However, many questions remain unanswered such as the cost effectiveness of such multidimensional profiling and the extent to which such profiling improves outcomes for individuals (119). It is vital that stakeholders across cancer science, medicine, and public health work together to ensure that all patients with cancer can equitably benefit from breakthroughs being made in cancer care by precision medicine approaches (120).

SIDEBAR 9

The National Cancer Institute's Precision Medicine Initiatives

NCI-MATCH (Molecular Analysis for Therapy Choice)

- Launched in 2015, NCI-MATCH is a precision medicine trial to evaluate whether the choice of treatment can be based on genetic changes present in tumors.
- The NCI-MATCH trial led FDA to approve the combination of dabrafenib and trametinib to treat any cancer carrying a genetic alteration in the *BRAF* gene (1,109).

Childhood Cancer Data Initiative (CCDI)

Launched in 2019, CCDI aims to:

- Gather data from every child, adolescent, and young adult (AYA) diagnosed with a childhood cancer, regardless of where they receive their care;
- Create a national strategy of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of childhood cancers;
- Develop a platform and tools to bring together clinical care and research data that will improve prevention, treatment, quality of life, and survivorship for childhood cancers.

Molecular Characterization Initiative (MCI)

- Launched in 2022 as a part of the CCDI, MCI is a national collaboration between the childhood cancer community, advocates, pediatric oncologists, researchers, data scientists, children and AYAs with cancer, and families.
- MCI provides state-of-the-art molecular characterization at the time of diagnosis that helps participants and doctors select the best and most appropriate treatment.

ComboMATCH (Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice)

Launched in 2023, ComboMATCH is a group of precision medicine cancer clinical trials, with the goal to determine whether treating cancer with combinations of drugs targeting specific genetic changes improves outcomes (110).

Reducing the Risk of Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- In the United States, 40 percent of all cancers are associated with modifiable risk factors.
- The significant decline in cancer mortality over the past three decades is largely attributable to reductions in smoking and increased cancer screening following the implementation of public health campaigns and policy initiatives.
- Nearly 20 percent of U.S. cancer diagnoses are related to excess body weight, unhealthy dietary patterns, alcohol intake, and physical inactivity.
- Many cases of skin cancer can be prevented by protecting the skin from ultraviolet radiation from the sun and indoor tanning devices.
- Nearly all cases of cervical cancer, as well as many cases of head and neck and anal cancers, can be prevented by HPV vaccination; many cases of liver cancer can be prevented by HBV vaccination.

Research in basic, translational, and population sciences has broadened our understanding of the factors that increase an individual's risk of developing cancer (see **Figure 7**, p. 39). Modifiable risk factors, including tobacco use, unhealthy diet, physical inactivity, UV exposure, alcohol consumption, pathogenic infections, and obesity contribute to the development of 40 percent of all cancers. Given that several of these risks can be avoided, many cases of cancer can potentially be prevented. The increased recognition of these risk factors, which also contribute to many other chronic diseases such as those of the cardiovascular system, will help local and national public health organizations increase prevention efforts, lessening the negative health and economic impact of these diseases, including cancer.

Between 1991 and 2020, the United States experienced a 33 percent decline in overall cancer mortality largely due to the implementation of public health campaigns and policy initiatives designed to reduce smoking and increase early detection of cancers (2). However, while smoking rates have declined, the increasing prevalence of other risk factors, including obesity among U.S. children and adults, is cause for concern. Additionally, there is a lack of widespread uptake in the United States of preventive interventions such as vaccination against cancer-causing viruses including human papillomavirus (HPV), which is the primary cause of cervical cancer. Addressing and reducing all modifiable risk factors, especially those on the rise such as obesity, are required to continue the downward trend in cancer-related deaths.

Globally, nearly half of all cancer deaths in 2019 were attributable to risk factors that include **smoking**, **alcohol**, and **high body-mass index** (121).

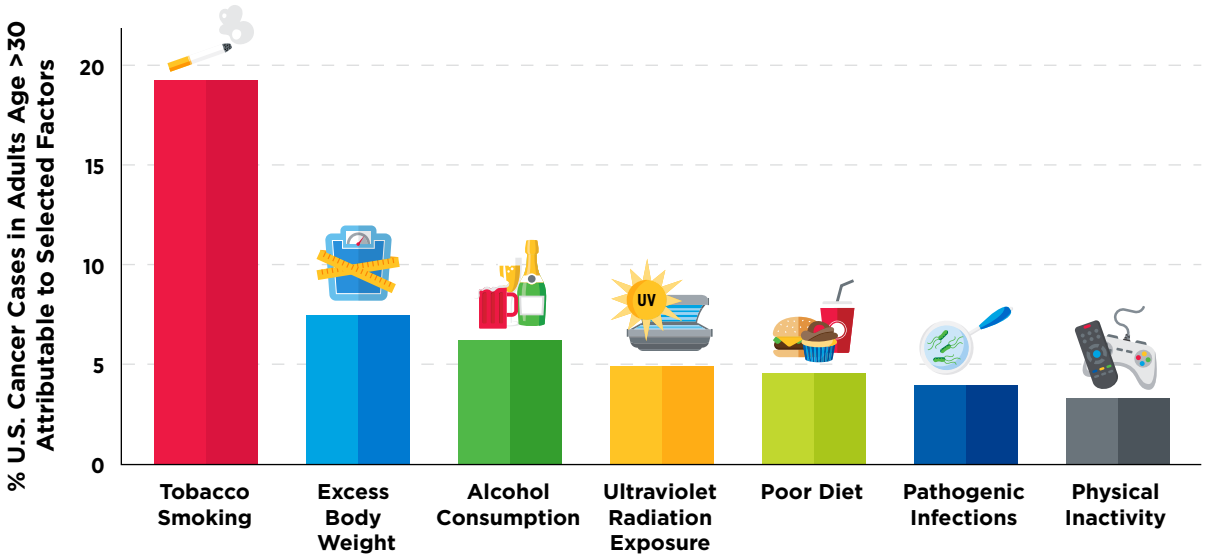
Prevalence of modifiable risk factors is higher in segments of the U.S. population that experience cancer disparities, such as racial or ethnic, and sexual and gender minorities, as well as other medically underserved populations. These inequities stem from decades of structural, social, and institutional injustices that have placed disadvantaged populations in unfavorable living environments and contributed to behaviors that increase cancer risk (see **Figure 2**, p. 19). For example, racial or ethnic minorities are more likely to live in areas that may have high levels of air pollution, no green spaces for physical activity, and/or little to no availability of healthy food options such as fresh fruits and vegetables. It is important that all stakeholders in public health work together to increase education and access to cancer prevention resources and eliminate the disproportionate burden of cancer risk factors in these populations.

Eliminate Tobacco Use

The use of tobacco products is the leading preventable cause of cancer and is associated with the development of 17 different types of cancer in addition to lung cancer. Nearly 20 percent

FIGURE 7

Modifiable Cancer Risks



Research has identified numerous factors that increase an individual's risk for developing cancer. By modifying behavior, individuals can eliminate or reduce many of these risks and thereby reduce their risk of developing or dying from cancer. Developing and implementing additional public health campaigns and policy initiatives can help further reduce the burden of cancers related to preventable cancer risk factors.

Adapted from (1).

of all cancer cases and 30 percent of all cancer-related deaths are caused by tobacco products (see **Figure 8**, p. 40). On average, people who smoke die ten years earlier than those who have never smoked (122,123). Research over the past 50 years has consistently demonstrated that byproducts released from smoking tobacco products, such as cigarettes, cause permanent cellular and molecular alterations which lead to cancer (124). Furthermore, smoking causes many other chronic conditions including chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis, emphysema, and many types of cardiovascular diseases. Secondhand smoke is estimated to cause 41,000 deaths each year among adults in the United States, with 7,300 of these due to lung cancer (123).

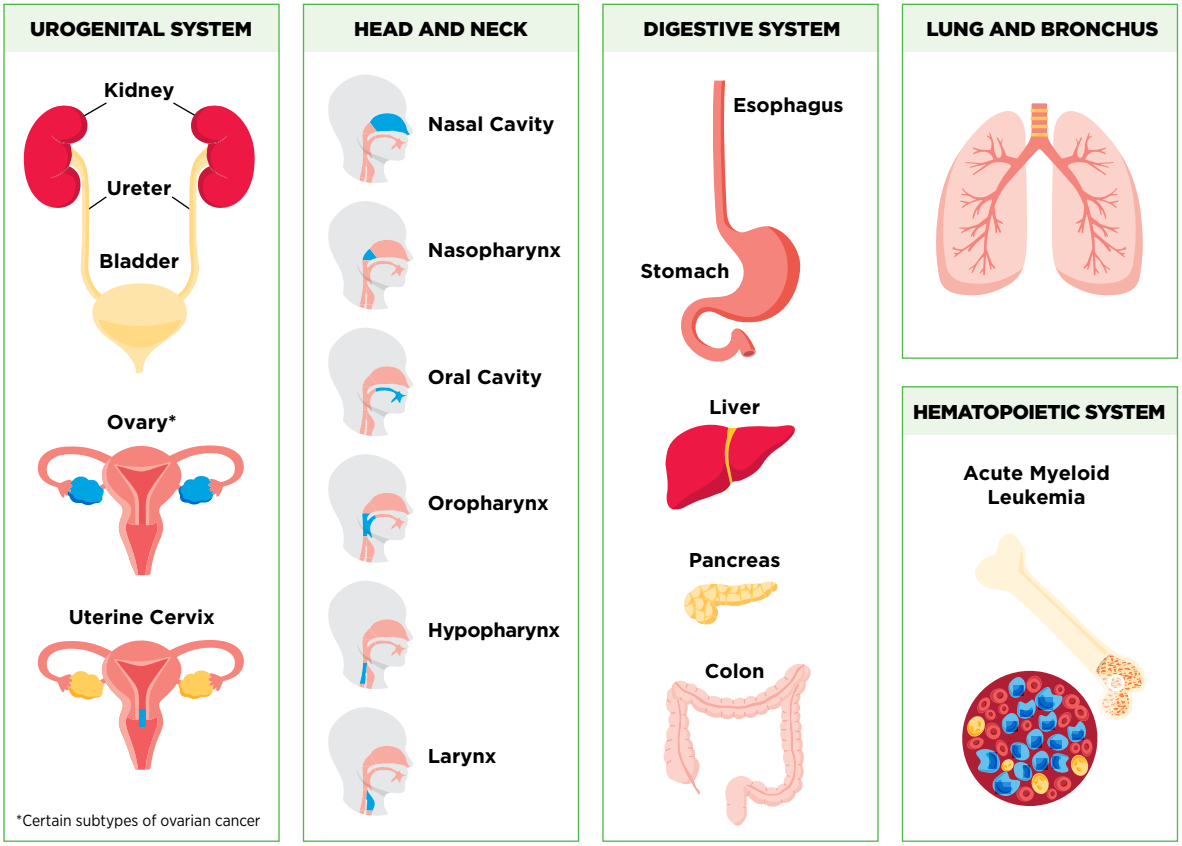
Thanks to nationwide tobacco control initiatives, cigarette smoking among U.S. adults has been on the decline. As of 2021, the most recent year for which such data are available, an estimated 46 million U.S. adults reported using any tobacco product (32). Of those, about 35.6 million reported using a combustible tobacco product (e.g., cigarettes, cigars, pipes) (32) (see **Sidebar 10**, p. 41). Rates of tobacco use among middle and high school students are also declining, with 16.5 percent of high school students (representing 2.51 million) and 4.5 percent of middle school students (representing 530,000) reporting having ever used tobacco products in 2022, which is down from 5.2 million high school students and 1.3 million middle school students in 2021, representing a 51 and 53 percent reduction, respectively (125,126). Despite the downward trends, these numbers are still of concern, as research shows that nine out of 10 adults who smoke cigarettes daily first try smoking by age 18, necessitating appropriate interventions among younger population to reduce the risk of continued tobacco usage as adults (127).

There is strong evidence that smoking cessation has both immediate and long-term health benefits (129-131). For instance, those who stop smoking reduce their risk of developing cancers of the larynx, oral cavity, and pharynx by half after 10 years of cessation. After 20 years, the risk of developing these cancers is lowered to the same level as someone who never smokes (132).

Lung cancer risk in people who stop smoking is decreased by 39 percent after five years. However, even 25 years after cessation, this group is three times as likely to develop lung cancer compared to those who have never smoked (133).

FIGURE 8

Beyond the Lungs: Cancers Caused by Smoking Tobacco



Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer. No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke. Use of smokeless tobacco (such as chewing tobacco and snuff) can cause oral, esophageal, and pancreatic cancer.

Figure adapted from (1).

Evidence-based interventions at local, state, and federal levels, including tobacco price increases, public health campaigns, marketing restrictions, cessation counseling, FDA-approved medications, and smoke-free laws, must be utilized to continue the downward trend of tobacco use (134).

Other combustible tobacco products (e.g., cigars), smokeless tobacco products (e.g., chewing tobacco and snuff), and water pipes (e.g., hookahs) are also associated with adverse health outcomes, including cancer (135-137).

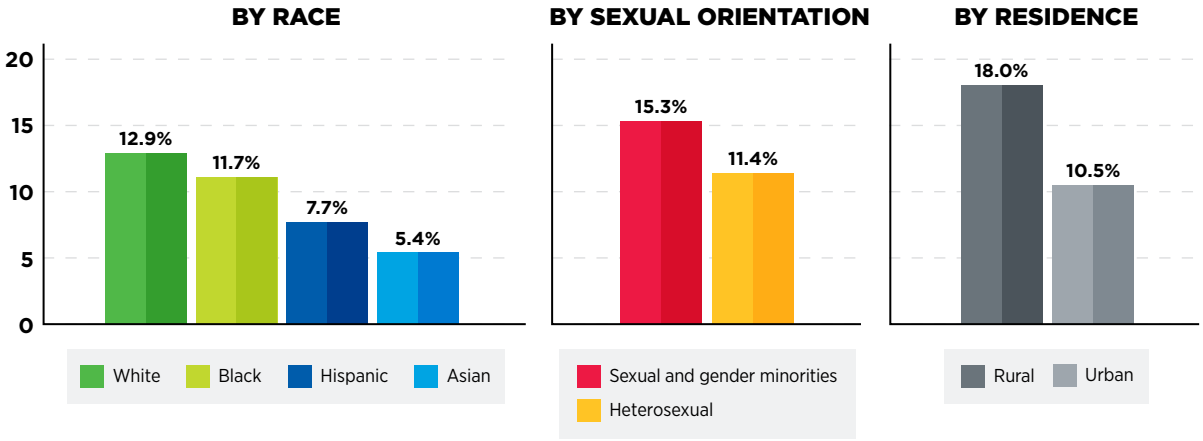
Electronic cigarettes (e-cigarettes) were first introduced into the U.S. market in 2006 and have gained popularity among those who smoke and those who have never smoked, especially among middle and high school students and young adults ages 18 to 24.

The landscape of e-cigarette devices has evolved over the years to include different types of products, such as prefilled pods (e.g., JUUL) or cartridge-based devices, and disposable devices (e.g., Puff Bar), among others. E-cigarettes can deliver nicotine, an extremely addictive substance that is harmful to the developing brain, at similar levels as traditional cigarettes (138,139). While e-cigarettes emit fewer carcinogens than combustible tobacco, they still expose individuals to toxic chemicals that can damage DNA and trigger inflammation (140-143). Unlike combustible cigarettes, e-cigarettes come in flavors, such as cotton candy and bubblegum, that appeal to youth and are key drivers of e-cigarette use among youth and young adults (144).

After years of increase, the use of e-cigarettes has started to decline among U.S. middle and high school students. Nearly 28 percent of high school students and 11 percent of middle school students reported using e-cigarettes in 2019. While these numbers have declined to 14.1 percent of high school students and 3.3 percent of middle school students in 2022, they are slightly higher than what was reported in 2021 (145,146).

SIDEBAR 10

Percentage of U.S. Adults Who Smoked Cigarettes in 2021



Adapted from (128).

Clearly, more work needs to be done to effectively curb the use of these products in young populations.

The FDA has implemented several restrictions on e-cigarettes in the past year (see **Leveraging Policy to Reduce Tobacco-related Illness**, p. 159). It is imperative that all stakeholders continue to work together and implement policies that reduce e-cigarette use among youth and young adults.

Maintain a Healthy Weight, Eat a Healthy Diet, and Stay Active

Nearly 20 percent of new cancer cases and 16 percent of cancer deaths in U.S. adults are attributable to a combination of excess body weight, poor diet, physical inactivity, and alcohol consumption (147). Being overweight or obese as an adult increases a person's risk for 15 types of cancer; being physically active reduces risk for nine types of cancer (see **Figure 9**, p. 42). Increased body mass index (BMI), which is a measure of body thickness based on height and weight, is often associated with an individual's likelihood of developing certain cancers (148-150). In addition, specific types of fat, such as abdominal obesity or a higher waist-to-hip ratio, may be a stronger risk factor (151,152). Being overweight or obese leads to long-lasting inflammation, abnormal levels of insulin, and higher than normal levels of sex hormones, all of which increase the risk of developing certain types of cancer (149).

Among U.S. adults, the rate of obesity from 2017 to 2020 was 41.9 percent (153). This is a 37 percent increase from the year 2000, when the rate was 30.5 percent (153). During this same time, severe obesity among U.S. adults nearly doubled, with an increase from 4.7 percent to 9.2 percent (153). As with smoking, adults who are obese have a high risk of many chronic diseases, including diabetes, cardiovascular disease, stroke, and cancer (1).

Of increasing concern is the rise in obesity among children and teens (2 to 19 years of age), increasing 300 percent in the past five decades, from five percent in the 1970s to approximately 19.7 percent during the period from 2017 to 2020 (154). Recent data show that being overweight or obese during childhood increases the likelihood of developing cancer as adults (155).

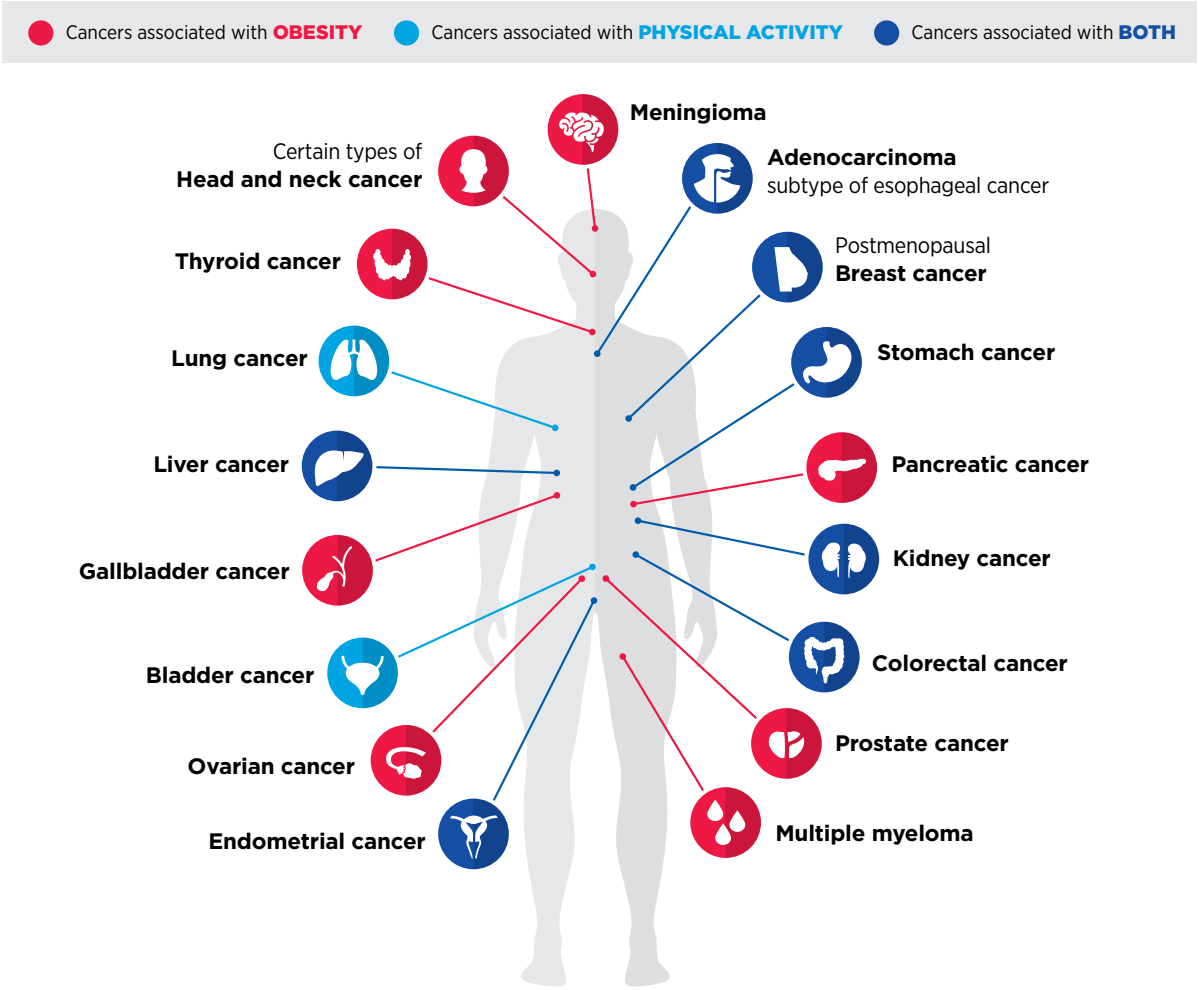
One emerging area of concern among public health experts is the recent rise in early-onset colorectal cancer that has been partially attributed to the rise in obesity (see **The Growing Population Burden of Cancer**, p. 20) (164). In a meta-analysis, which examined 30 studies on early-onset colorectal cancer risk factors, being overweight or obese increased the likelihood of developing early-onset colorectal cancer by 1.2 and 1.5 times, respectively, compared to maintaining a healthy weight (165). Understanding how modifiable risk factors like obesity, unhealthy diet, and lack of exercise are contributing to the rise in early-onset colorectal cancer is vital for establishing effective prevention efforts.

Weight loss interventions have proven to be effective in reducing or eliminating the risk of cancers associated with obesity. As one example, bariatric surgery, a term used to describe a collection of procedures that are done to help people who are obese lose

In a study of over 69,000 women, researchers found that **surgical weight loss interventions** reduced the risk of developing breast cancer (169).

FIGURE 9

Reasons to Maintain a Healthy Weight and Stay Active



Fifteen types of cancer—the adenocarcinoma subtype of esophageal cancer; certain types of head and neck cancer; advanced prostate cancer; meningioma, a low grade brain tumor; multiple myeloma; and colon, rectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese. Being physically active lowers the risk of nine cancers—bladder, breast (postmenopausal), colon, endometrial, esophageal, kidney, liver, lung, and stomach. There is growing evidence that physical fitness may also reduce the risk of developing additional types of cancer. Cancers associated with obesity are shown in red; cancers associated with physical activity are shown in light blue; cancers that are associated with both are shown in dark blue.

Data from (156-162). Figure adapted from (163).

weight, has been shown to lower the risk of developing and/or dying from certain obesity-associated cancers (166-168). While further research is needed to elucidate whether bariatric surgery can effectively reduce the burden of all obesity-related cancers, identifying equitable strategies including lifestyle and therapeutic interventions to address obesity must certainly be a top priority for U.S. public health.

Another effective intervention to reduce weight is through increased physical activity. Unfortunately, many U.S. adults do not meet the minimum recommended physical activity guidelines (see **Sidebar 11**, p. 43). According to recent data from CDC, only 25 percent of individuals met the minimum amount of aerobic and muscle-strengthening exercise in 2020 (170). This is concerning because physical activity can reduce the risk of nine types of cancer, with research indicating that, annually, over 46,000 U.S. cancer cases could potentially be avoided if everyone met these guidelines (see **Sidebar 11**, p. 43) (171).

SIDEBAR 11

Physical Activity Guidelines

Incorporation of regular physical activity into daily life is one of the most important steps people can take to improve their health, including reducing cancer risk. The recommended level of physical activity varies depending on age and preexisting medical conditions.

	PRE-SCHOOL AGED CHILDREN (3-5 years)	PREGNANT WOMEN	ADOLESCENTS (Under 18 years)	ADULTS (18-64 years)	OLDER ADULTS (65+ years)
	AEROBIC ACTIVITY				
Should be encouraged to move and engage in active play at all levels of intensity throughout the day.		150 minutes per week	60 minutes per day	150 minutes moderate intensity per week or 75 minutes vigorous intensity per week	
	STRENGTH TRAINING				
		2 days per week	3 days per week	2+ days per week	2+ days per week

AEROBIC ACTIVITY

Cardiovascular exercise that gets your heart pumping

Moderate intensity

Includes activities in which one can still talk without pausing for breaths, such as:

- Walking
- Pushing lawnmower
- Water aerobics
- Pickle ball

Vigorous intensity

Includes activities during which it is hard to speak more than a few words before catching breath, such as:

- Running
- Swimming fast
- Cycle fast or on hilly terrain

STRENGTH TRAINING

Includes activities which work muscles and core by doing repetitions or sets of movements, such as:

- Yoga
- Martial arts
- Tai chi
- Pilates
- Lifting weights
- Using resistance equipment

Cancer survivors should consult their physicians and follow modified guidelines adapted for their personal health, specific cancers, and treatment.

Developed from (172).

Based on a recent study, people who engage in four to five minutes of vigorous physical activity daily can reduce their cancer risk by up to 32 percent (173). Another study among older adults who engaged in several types of exercise, including running, racquet sports, walking, golf, swimming, and cycling, found that all forms of exercise reduced all-cause, cardiovascular, and cancer mortality, compared to those who did not participate in these activities (see **Sidebar 11**, p. 43) (174). It is important to note that the type of exercise is not as important as getting the recommended amount of physical activity.

A 20-year prospective study found that people who engaged in regular, **high-intensity aerobic workouts** were 73 percent **less likely to develop metastatic cancers** (175).

Researchers found that the use of low-cost activity trackers led **users to walk 40 additional minutes per day** (178).

There are many barriers that may prevent individuals from being physically active, including cost and access to fitness facilities, lack of green spaces, and family obligations (176). These barriers are exacerbated in racial and ethnic minorities and other medically underserved populations. Based on recent data, physical inactivity is higher in Hispanics (31.7 percent) and non-Hispanic Blacks (30.3 percent), compared to non-Hispanic Whites (23.4 percent) (177). There are also geographic disparities, with only 16 percent of people in suburban and rural areas meeting the recommended physical activity guidelines, compared to 27.8 percent of those living in urban areas (170).

Developing widespread campaigns to increase physical activity in the U.S. population is vital if we are to change the current trends. As one example, The Active People, Healthy Nation initiative aims to help 27 million people become more physically active by 2027 by designing activity-friendly communities, encouraging physical activity at school, and engaging community leaders to implement relevant programs to encourage physical activity.

Poor diet, consisting of processed foods and lacking fresh fruits or vegetables, is responsible for the development of about five percent of all cancers, with several studies demonstrating a link between consumption of highly processed foods and cancer incidence (179). It is therefore concerning that U.S. adults consumed about seven percent more highly processed foods in 2017-2018 than they did in 2001-2002 (180).

Highly processed foods lack fiber and include high amounts of added sugar, salt, fats, preservatives, and additives in their ingredients (see **Sidebar 12**, p. 45). Research has shown that high consumption of ultra-processed foods is associated with an increased risk of colorectal cancer (181). On the other hand, a diet rich in fresh fruits and vegetables, nuts, whole grains, and fish can help lower the risk of developing certain cancers and many other chronic conditions. For instance, one study of nearly 80,000 men from diverse backgrounds showed that adherence to a healthy diet lowered risk for certain types of colorectal cancers (182). There is growing appreciation of following healthy and balanced dietary patterns rather than eating more of a specific nutrient. For instance, a Mediterranean Diet emphasizes consumption of plant-based foods and healthy fats, which allows individuals to customize their diet to fit their tastes and preferences.

The widespread availability and low cost of fast food—food that can be prepared quickly and easily and is sold in restaurants and snack bars as a quick meal or to be taken out—led to 37 percent of U.S. adults (ages 40 to 59) and 45 percent of U.S. young adults (ages 20 to 39) consuming these on any given day during 2013-2016 (184). Unfortunately, fast foods are highly processed, calorie dense, high in salt content, and low in fiber, making them of poor nutritional value. It is also concerning that fast food consumption is higher among racial or ethnic minorities with 43 percent of non-Hispanic Black adults versus 36 percent of non-Hispanic White adults consuming fast food between 2013 and 2016, the most recent timeframe for which these data are available (184).

Disparities in diet quality among different segments of the U.S. population can be attributed to socioeconomic and geographic factors, which contribute to food insecurity. Food insecurity is defined by the United States Department of Agriculture (USDA) as the lack of access by all people in a household at all times to enough food for an active, healthy life. Studies show that food insecurity is higher among racial or ethnic minorities and those who live in poverty. These communities are often located in neighborhoods that are considered "food deserts," which are areas that have low availability of healthy foods like fresh fruit and vegetables and an abundance of fast-food options. Community-driven initiatives administered through key partners, such as faith-based organizations, schools, and local food retailers, are one mechanism to promote healthy eating.

Sugar-sweetened beverages are a major contributor to caloric intake among U.S. youth and adults, and there are emerging data indicating that consumption of sugar-sweetened beverages may be associated with an increased risk of cancer (4). In certain rural areas, for example the Appalachia region, local interventions have led to a reduction in consumption of sugar-sweetened beverages, and increased consumption of vegetables (185). The Philadelphia Beverage Tax on sugar-sweetened beverages, implemented in 2017, increased the cost of sodas and juices that contain sugar by 1.5 cents per ounce. The tax led to demonstrated reductions in the consumption of sugar-sweetened beverages (186), with one study indicating as much as a 42 percent drop in the sale of these types of beverages after two years (187). The tax revenue generated is used to fund early-education programs (including free universal pre-K), healthy messaging, and upgrades to playground equipment (188). Pilot initiatives like these need to be closely examined to determine their long-term health effects and impact on diet, obesity, and cancer burden.

Reduce Risk of Diabetes

Diabetes affects 11.3 percent of the U.S. population, equating to 37.3 million people (189). Evidence shows that having type 1 or type 2 diabetes increases the risk of developing liver, pancreatic, endometrial, colorectal, breast, and bladder cancers. Type 2 diabetes, a condition in which the body cannot regulate sugar properly, can be attributed to genetic factors as well as modifiable risk factors, some of which are also risk factors for cancer, such as obesity, poor diet, physical inactivity, and smoking. Recent studies have shown that many health conditions that are common among those with diabetes, including high

SIDEBAR 12

Making Healthy Food Choices: Nutrition Labels

Nutrition labels found on food packaging break down the number of calories, and amount of carbohydrates, fat, fiber, protein, and vitamins per serving of food. Because these labels are required to be on most packaged foods, it is easy to compare different products quickly. In general, foods with high amounts of vitamins, minerals, and fiber are the healthiest options. It is better to avoid products that are high in sodium, added sugars, saturated and trans fats, and have added preservatives. For more information about the newest guidance on reading food labels, visit **www.fda.gov/NewNutritionFactsLabel**.

NUTRITION FACTS INFORMATION

1. The number of calories a food contains is **directly related to how much energy it contains**.
2. While fat is a central component of nutrition, pay close attention to the levels of saturated and trans fats commonly found in processed foods. These types of fats **can raise cholesterol levels, increase risk of chronic conditions, and lead to obesity, which increases risk of cancer**.
3. Cholesterol is a type of fat that the body needs to work properly. However, **high levels of cholesterol can lead to heart disease, stroke, and other problems**.
4. Foods high in sodium including processed meats and fast foods should be eaten in limited amounts. For instance, processed meats such as hot dogs, bacon, and salami **can increase risk for colorectal and possibly other cancers**.
5. **Carbohydrates are an essential part of food** because when broken down, they turn into a type of sugar the body uses as a source of energy. Therefore, both the amount and the type of carbohydrate are equally important.
   - White bread, pastries, sodas, and other **highly processed or refined foods are sources of unhealthy carbohydrates** that contribute to weight gain and promote diabetes, which **can increase the risk of cancer**.
   - **Healthy sources of carbohydrates such as whole grains, vegetables, fruits, and beans are also sources of vitamins, minerals, fiber, and other nutrients.** It is recommended that a diet consist of healthy carbohydrates, with vegetables and fruits taking up about half of the plate, with whole grains filling up about one fourth of the plate.
6. Sugars can be present in all types of foods and occur naturally in fruits, honey, and milk. However, one should be aware of foods that contain added sugars, which are often from refined sources. **High levels of added sugar** like those in sugar-sweetened beverages **contribute to prolonged elevated blood sugar and insulin resistance** increasing the chance of developing diabetes and becoming overweight, which **can increase the risk of cancer.**
7. It is recommended that individuals eat at least 30 grams of fiber every day. Common sources of fiber include whole grains, fruits, and vegetables (183). A diet rich in these food sources has a low energy density and **promotes a healthy weight**.
8. Along with carbohydrates and fats, protein is a **primary source of energy**. Proteins contain amino acids that can be classified as either essential or nonessential. **Essential amino acids are vital in a diet** because our body cannot make them. Always try to eat protein from sources such as quinoa, soy, and buckwheat that contain all 20 amino acids.
9. Vitamins and minerals are **essential food components** derived from different sources. Vitamins are derived from plants and animals and cannot be made by the body (with the exception of vitamin D). Vitamins have many functions in the body including **keeping nerves healthy, helping the body get energy from food, and managing blood clots**. Minerals are derived from rocks, soil, or water but can be present in foods. Minerals like fluoride or calcium **strengthen bones and prevent cavities**. While getting vitamins and minerals from supplements doesn't reduce cancer risk, eating a diet rich in vitamins and minerals from fruits and vegetables **drastically reduces cancer risk**.

Nutrition Facts

8 servings per container

Serving size **2/3 cup (55g)**

Amount per serving

1 **Calories** **230**

	% Daily Value*
Total Fat 8g	**10%**
2 Saturated Fat 1g	**5%**
2 *Trans* Fat 0g	
3 **Cholesterol** 0mg	**0%**
4 **Sodium** 160mg	**7%**
5 **Total Carbohydrate** 37g	**13%**
6 Dietary Fiber 4g	**14%**
7 Total Sugars 12g	
7 Includes 10g Added Sugars	**20%**
8 **Protein** 3g	
9 Vitamin D 2mcg	10%
9 Calcium 260mg	20%
9 Iron 8mg	45%
9 Potassium 240mg	6%

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

SIDEBAR 13

Guidelines for Alcohol Consumption

The U.S. Department of Agriculture and U.S. Department of Health and Human Services, *Dietary Guidelines for Americans, 2020-2025*, do not recommend that individuals who do not drink alcohol start drinking for any reason. There are also some people who should not drink at all, such as those who are pregnant or might be pregnant; are under the legal age for drinking; have certain medical conditions or are taking certain medications that can interact with alcohol; and if they are recovering from an alcohol use disorder or if they are unable to control the amount they drink.

If adults age 21 and older choose to drink alcoholic beverages, **drinking less is better for health than drinking more**. The guidelines recommend (199):

IF ALCOHOL IS CONSUMED, IT SHOULD BE DONE IN MODERATION.

Moderate drinking

≤ 1 drink per day for women

≤ 2 drinks per day for men

Only by **adults of legal drinking age**

The following are reference beverages that are one alcoholic drink-equivalent:

12 fl oz of regular beer (5% alcohol)

5 fl oz of wine (12% alcohol)

1.5 fl oz of 80 proof distilled spirits (40% alcohol)

ACCORDING TO THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM:

Heavy drinking

≥ 3 drinks on any day or **≥ 7 drinks per week** for women

≥ 4 drinks on any day or **≥14 drinks per week** for men

Binge drinking

≥ 4 drinks within 2 hours for women

≥ 5 drinks within 2 hours for men

Excessive alcohol consumption

Includes **binge drinking**, **heavy drinking**, and **any drinking** by **pregnant women** or those **under 21** years of age.

Adapted from (1).

levels of insulin and inflammation, may also increase the risk of breast, colorectal, prostate, endometrial, liver, and ovarian cancers, regardless of an individual's BMI (190). Continuing to understand the mechanisms by which diabetes contributes to cancer risk may help identify opportunities for intervention.

Encouragingly, keeping blood sugars low through eating a healthful diet rich with vegetables, fruits, and whole grains; engaging in physical activity; reducing or eliminating alcohol consumption; and stopping smoking can significantly reduce the risk of cancer in people with diabetes. It is essential that patients with diabetes be aware of their increased cancer risk and undergo recommended age- and sex-appropriate cancer screenings.

Limit Alcohol Consumption

The consumption of alcohol is linked to more than 200 diseases and increases the risk of six different types of cancer including certain types of head and neck cancer, esophageal squamous cell carcinoma, and breast, colorectal, liver, and stomach cancers. Nearly four percent of cancers diagnosed worldwide in 2020 can be attributed to alcohol consumption (191). In the U.S., it is estimated that from 2013 to 2016, 75,000 cancer cases and 19,000 cancer deaths were linked to alcohol (192). All alcoholic beverages pose a risk for cancer development because they contain ethanol, which can modulate hormones, and its byproducts can damage DNA, which increases the risk of developing cancers (193).

The greatest risks are associated with long-term alcohol consumption and binge-drinking, i.e., when large amounts of alcohol are consumed in a short period of time (194). Even light intake of alcohol can increase an individual's risk for certain cancers, while moderate drinking can increase the risk of developing certain cancers of the head and neck, breast, and colon and rectum (195-198). Following guidelines for alcohol consumption (see **Sidebar 13**, p. 46) can help to lower the risk of developing alcohol-related cancers.

Research indicates that those who reduce or stop drinking alcohol can decrease their risk of developing alcohol-related

93 percent of Americans recognize tobacco as a risk factor for cancer, while **only 39 percent of Americans associate alcohol with cancer risk** (202).

cancers by eight percent and can reduce their risk of all cancer by four percent compared to those who sustain or increase their consumption of alcohol (200, 201). Public messaging campaigns (such as cancer-specific warning labels displayed on alcoholic beverages) must be considered along with effective clinical strategies to reduce the burden of alcohol-related cancers.

Future efforts focused on evidence-based policy interventions, such as regulating the number of alcohol stores in a given area, and increased taxes and prices need to be implemented to curb the consumption of alcohol.

Protect Skin from UV Exposure

Ultraviolet (UV) radiation is a type of light emitted primarily from the sun but also from artificial sources, such as tanning beds. Exposure to UV radiation can lead to the development of skin cancers, including basal cell carcinoma, squamous cell carcinoma, and melanoma, which is the most aggressive form of skin cancer. In fact, UV radiation accounts for 95 percent of skin melanomas and six percent of all cancers (147). This is because UV radiation can damage cellular DNA with continued exposure leading to cancer.

Anyone can develop skin cancer, but some people are at a higher risk, especially those who are light skinned and get easily sunburned.

It has been reported that there is a lack of understanding in the U.S. population regarding how skin cancer develops and when to use sun protection (203). According to data from the CDC, 29 percent of U.S. adults and 64 percent of adolescents experienced sunburn at least once in the past year in 2021 (204,205). This is concerning, as severe sunburns increase the risk of developing all three types of skin cancer (up to two and a half times for melanoma), compared to no history of severe sunburn (206). One study reported that women who experienced at least five episodes of severe sunburns between the ages of 15 and 20 years were 80 percent more likely to develop melanoma later in life, compared to those who did not experience sunburns (207).

Indoor tanning decreased from 10 percent in 2007 **to four percent** in 2018 **among U.S. adults** (192) and from 15.6 percent in 2009 **to 5.6 percent** in 2017 **among U.S. high school students** (193).

SIDEBAR 14

Ways to Protect Your Skin

To reduce the risk of three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—the U.S. Centers for Disease Control and Prevention recommends the following measures:

Seek shade and **limit time in the sun**, especially during peak sun hours (10:00 a.m. to 4:00 p.m.).

Wear clothing that covers arms and legs; some clothing is designed to provide protection from the sun.

Wear a **wide-brimmed hat**.

Wear **wrap-around sunglasses**.

Apply the recommended amount of a **sunscreen before going outside** (even on slightly cloudy or cool days); it takes about 1 ounce to fully cover the body; Look for sunscreen that is **SPF 30 or higher**, offers "broad-spectrum" protection, and is water resistant. Sunscreen should be applied 15 minutes prior to going outside.

Avoid indoor tanning with UV devices such as sunlamps, sunbeds, and tanning booths.

One common misconception is that people cannot get sunburned on cloudy days. However, up to 80 percent of the sun's harmful UV rays can penetrate clouds. It is recommended that individuals practice sun-safe habits anytime they are outside to limit exposure to harmful UV radiation (see **Sidebar 14**, p. 47).

It is encouraging that the use of tanning beds, particularly among U.S. youth, has dramatically decreased in the past decade.

TABLE 2

Cancer-causing Pathogens

BACTERIA

Pathogen	Cancer types caused by the pathogen	Number of global cancer cases
Helicobacter pylori	Stomach cancer and non-Hodgkin lymphoma	810,000

PARASITES

Pathogen	Cancer types caused by the pathogen	Number of global cancer cases
Clonorchis sinensis and Opisthorchis viverrini	Cholangiocarcinoma	3,500
Schistosoma haematobium	Bladder cancer	Not available

VIRUS

Pathogen	Cancer types caused by the pathogen	Number of global cancer cases
Epstein-Barr Virus (EBV)	Hodgkin lymphoma, certain types of non-Hodgkin lymphoma, and nasopharyngeal cancer	156,600
Hepatitis B Virus (HBV)	Hepatocellular carcinoma and other cancers	360,000
Hepatitis C Virus (HCV)	Hepatocellular carcinoma and other cancers	156,000
Human Herpes Virus type-8 (HHV-8; also known as Kaposi sarcoma herpes virus)	Kaposi sarcoma	42,000
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	Not available
Human Papillomavirus (HPV)	Anal, cervical, head and neck, larynx, oral, oropharyngeal, penile, vaginal, and vulvar cancers	690,000
Human T-cell Lymphotrophic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma	3,600
Merkel Cell Polyomavirus (MCV)	Skin cancer	Not available

Adapted from (1).

Implementing legislation that restricts the use of tanning beds among youth is important to prevent use of these devices, especially because youth who use tanning beds by 17 years of age are twice as likely to continue using these devices as adults (208). Currently, 44 states and the District of Columbia either ban or regulate the use of indoor tanning devices by minors (209). All states should enact legislation banning indoor tanning for minors, to continue the downward trend of tanning bed usage, especially among youth.

Prevent and Eliminate Infection from Cancer-causing Pathogens

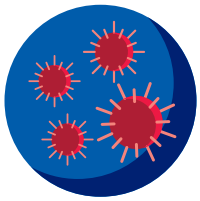
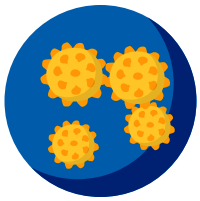
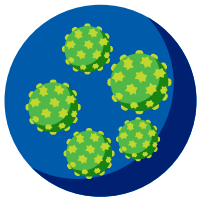
Cancer-causing pathogens (bacteria, viruses, and parasites) increase a person's risk for several types of cancer (see **Table 2**, p. 48). Infection with these agents can change the way a cell behaves, weaken the immune system, and cause chronic inflammation, all of which can lead to cancer. In the United States, about three percent of all cancer cases are attributable to infection with pathogens (147). Globally, an estimated 13 percent (2.2 million) of all cancer cases in 2018 were attributable to pathogenic infections, with more than 90 percent of these cases attributable to four pathogens: human papillomavirus (HPV), hepatitis B (HBV), hepatitis C (HCV), and *Helicobacter pylori* (212).

Individuals can significantly lower their risks by protecting themselves from infection or by seeking treatment, if available, to eliminate an infection (see **Sidebar 15**, p. 49).

Human papillomavirus is a group of more than 200 related viruses that are responsible for almost all cervical cancers, 90 percent of anal cancers, and 70 percent of oropharyngeal cancers, as well as most penile, vaginal, and vulvar cancers. While most

SIDEBAR 15

Ways to Reduce Cancer Risk from Pathogens

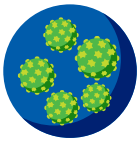
PATHOGEN	WAYS TO PREVENT INFECTION	WAYS TO ELIMINATE OR TREAT INFECTION	SPECIFIC RECOMMENDATIONS
Helicobacter pylori 	Avoid exposure through good hygiene and sanitation	Treatment with a combination of antibiotics and a proton-pump inhibitor can eliminate infection	CDC recommends testing and treatment for people with active or a documented history of gastric or duodenal ulcers, low-grade gastric MALT lymphoma, or early gastric cancer that has been surgically treated
Hepatitis B virus (HBV) 	HBV vaccination Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment of those chronically infected with antiviral drugs rarely eliminates infection but does slow virus multiplication; this slows the pace at which liver damage occurs and thereby reduces risk for liver cancer	Vaccination is recommended as part of the childhood vaccination schedule and is recommended for adults ages 19 to 59. CDC recommends screening for HBV infection in adults age 18 years and older at least once in their lifetime using a triple panel test.
Hepatitis C virus (HCV) 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment with any of several antiviral drugs can eliminate infection	There is consensus in recommendations from CDC and USPSTF for universal screening of all adults ages 18 to 79.
Human papillomavirus (HPV) 	Three FDA-approved vaccines Practice safe sex, although this may not fully protect against infection	None available	CDC recommends HPV vaccination for boys and girls age 11 or 12; recommendations for other groups can be found in **Sidebar 16**, p. 50)

CDC, Centers for Disease Control and Prevention; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force.
Adapted from (1).

HPV infections do not cause cancer, those that are persistent and with high-risk HPV virus types can lead to cancer. These high-risk HPVs cause three percent of all cancers in women and two percent in men in the United States (213). Globally, HPV-related cancers comprise about five percent of all cancers (214).

SIDEBAR 16

HPV Vaccination Recommendations



Thirteen strains of human papillomavirus (HPV) can cause cancer:

HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66.

U.S. Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP) recommend:

- **Two doses of HPV vaccine**, given at least six months apart, for **adolescents younger than age 15** (except immunocompromised persons).
- **Three doses of HPV vaccine** for adolescents and **young adults ages 15 to 26** and for **people with weakened immune systems**.
- **Shared decision-making** through discussion with health care providers for **adults ages 27 to 45**; if an individual chooses to be vaccinated, three doses of HPV vaccine.

Adapted from (1).

Although there are **three FDA-approved HPV vaccines**, Gardasil (first approved in 2006), Cervarix (first approved in 2009), and Gardasil 9 (first approved in 2014), only one (Gardasil 9) is currently being distributed in the United States.

Gardasil 9

Protects against infection with 9 strains of HPV: HPV6, 11, 16, 18, 31, 33, 45, 52, and 58.

FDA approved for:

- Preventing anal, cervical, head and neck, vaginal, and vulvar cancers and precancers, as well as genital warts.
- Vaccination of males and females ages 9 to 45.

Fortunately, the most recently approved vaccine for HPV, Gardasil 9, protects against nine of the 13 different types of cancer-causing HPV strains. This vaccine has been extremely effective in reducing the incidence of cervical cancer among 20- to 24-year-old women, the first group to become eligible after the U.S. approval of the vaccine in 2006. The most recent data show that between 2012 and 2019, rates of cervical cancer declined by 65 percent among U.S. women in their early 20s, compared to only a 33 percent reduction in the previous decade (2005-2012) (28).

The HPV vaccine is approved for males and females ages nine to 45, with recommendations for the first doses beginning at age 11 to 12 (see **Sidebar 16**, p. 50). Despite the positive impact of the vaccine on reducing cervical cancer incidence, the uptake of the HPV vaccine has been suboptimal in the United States. In 2021, only 76.9 percent of adolescents ages 13 to 17 had received one dose of the HPV vaccine and only 61.7 percent had received the recommended two doses (215). This stands in sharp contrast to other countries, such as the United Kingdom, where high uptake of HPV vaccination among 12- to 13-year-old girls has led to an 87 percent reduction in cervical cancer among women in their 20s (216).

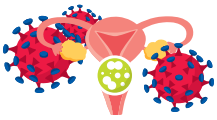
Programs designed to increase rates of HPV vaccination in the U.S., such as The Healthy People Initiative, which aims to vaccinate 80 percent of the eligible population, using strategies, including the implementation of vaccination information systems, patient reminders, and vaccination programs in schools can have immense public health benefit (217).

Chronic infection with HBV and HCV, viruses that cause liver inflammation and damage, can lead to liver cancer and other malignancies including non-Hodgkin lymphoma (NHL), if left untreated (218,219). After new reported cases of HBV remained stable through 2013 until 2019, there was an abrupt decrease of 32 percent reported cases in 2020, potentially attributable to the COVID-19 pandemic, which may have led to reduced testing but not necessarily reduced infections (220). In contrast, cases of HCV have doubled since 2013, with an increase of 15 percent between 2019 and 2020 (220). These numbers are concerning, as HBV is preventable with vaccination and HCV can be cured using antiviral medications.

To eliminate viral hepatitis as a public health threat, the U.S. Department of Health and Human Services released the *Viral Hepatitis Strategic Plan for the United States: A Roadmap to Elimination (2021-2025)*. The primary goals listed in the report are to prevent new infections, improve hepatitis-related health outcomes for infected individuals, reduce disparities and health inequities related to hepatitis, improve surveillance of viral hepatitis, and bring together all relevant stakeholders in coordinating efforts to address the hepatitis epidemic.

Individuals infected with human immunodeficiency virus (HIV) have an elevated risk of Kaposi sarcoma, NHL, and cervical cancer; these are called AIDS-defining cancers because they are

Globally, **5 percent of all cases of cervical cancer** are attributable to HIV (53).



more likely to occur in people who are infected with HIV, which is the virus that causes AIDS (221). This higher risk is attributable to HIV infection, which weakens the immune system. Prior to highly active antiretroviral therapy (HAART) in 1996, people infected with HIV had a 2,800-fold higher risk of Kaposi sarcoma compared to the general population (222). Since HAART, there has been a steady decline in incidence of Kaposi sarcoma; however, rates remain 800-fold higher than in the general population (223). As the population living with HIV continues to age, the burden of cancers, particularly non-AIDS-defining cancers (such as anal, liver, and lung cancers) will continue to rise (224). One study reported that incidence of lung cancer in people with HIV age 60 years and older is higher than the two most common AIDS-defining cancers, NHL and Kaposi sarcoma (225).

Studies have shown that **first responders** who were **involved in the rescue and recovery efforts of the 9/11 terrorist attacks** in New York City have **increased incidence of melanoma, prostate cancer, thyroid cancer, and tonsil cancer** (228). This may be due to higher levels of precancerous mutations in their blood cells when compared to first responders who did not participate in these efforts (229).

Limit Exposure to Environmental Risk Factors

Environmental pollutants are encountered in the air, drinking water, and food making them nearly impossible to avoid. Federal agencies, including the Environmental Protection Agency and Department of Health and Human Services, set guidelines for the acceptable exposure limits allowed in the environment. However, some individuals experience higher levels of exposure to certain pollutants due to their occupation, living conditions, or daily activities. Exposure to higher than acceptable levels of certain pollutants, without appropriate protection, can increase the risk of certain diseases. Environmental carcinogens, which are substances that can lead to cancer and are present in the environment, include arsenic, asbestos, radon, lead, radiation, and other chemical pollutants. The International Agency for Research on Cancer (IARC) and the U.S. National Toxicology Program (NTP) are both responsible for evaluating substances and exposures and classifying them as carcinogens at the global and national level, respectively.

Higher than normal levels of exposure to carcinogens have led IARC to classify certain occupations, such as firefighting and painting, and work environments, such as iron and steel foundries or working around welding fumes, as class 1 carcinogens, meaning they are cancer-causing to humans (see **Sidebar 17**, p. 52).

It can be difficult for some segments of the U.S. population to avoid or reduce their exposure to environmental carcinogens. For instance, racial or ethnic minorities and people living in poverty are often at increased risk of being exposed to high levels of air pollution, which the IARC has designated as a potential cause of cancer in humans. One type of air pollution termed particle pollution refers to a mix of tiny solid and liquid particles that are in the air we breathe. Nearly 36 percent of the U.S. population, representing 119.6 million people, live in places with unhealthy levels of particle pollution (236). New laws, regulations, and policies to reduce the release of pollutants into the atmosphere are necessary to minimize the long-term, adverse health effects of air pollution, including cancer.

Other exposures including chronic stress, lack of sleep, and night-shift work have also been shown to increase a person's risk of developing certain types of cancer (237).

The CDC reports that about 11 million adults in the U.S. frequently work night shifts, with certain groups such as men, and Black and non-Hispanic individuals, more likely to do this type of work. In one recent study, researchers found that women age 50 or older who had both day and night shifts were twice as likely to develop breast cancer compared to those who only worked day shifts (238). Although the underlying mechanisms are not clear, researchers believe that disruption of the body's circadian rhythm (i.e., the internal clock) can alter biological processes that normally help prevent cancer development. Emerging research indicates that avoiding lighting that disrupts circadian rhythms, for example, lighting that is low in blue light may help reduce cancer risk (239-241). Long-term research is needed to understand how exposure to certain light sources, particularly at night, may contribute to cancer risk.

As we learn more about environmental and occupational cancer risk factors and identify those segments of the U.S. population who are exposed to these factors, new and equitable policies need to be developed and implemented to reduce cancer risk and improve the health of all populations.

In 2023, **63.7 million people** living in the United States were **exposed to daily, unhealthy spikes in particle pollution** (236).

SIDEBAR 17

Occupation and Cancer Risk in Firefighters

Firefighters are at a greater risk of developing several types of cancer because of the constant exposure to smoke and other hazardous materials (226,227). In 2022, IARC characterized firefighting as a class 1 carcinogen because there is sufficient evidence that firefighters are more likely to develop many types of cancers.

THE RISKS

All firefighters, regardless of their status as a career or a volunteer firefighter, are **exposed to a wide range of carcinogenic compounds** due to the environmental conditions in which they work (230). Modern homes and furnishings are made of synthetic and plastic materials, which release more unburned particulates (i.e., smoke) compared to natural products made from wood and cloth. Even after the fire is extinguished, carcinogenic particulates remain on turnout gear and equipment, which can be brought back to the fire apparatus and fire station if appropriate decontamination procedures are not followed.

THE CANCERS

Reports indicate that firefighters have a nine percent higher risk of being diagnosed with, and a 14 percent higher risk of dying from cancer compared to the general U.S. population. **Firefighters have a higher risk of being diagnosed with certain specific cancer types, including**:

- **Testicular cancer** 2X greater
- **Thyroid cancer** 2.1X greater
- **Mesothelioma** 2X greater
- **Multiple myeloma** 1.5X greater
- **Non-Hodgkin lymphoma** 1.5X greater
- **Leukemia** 1.14X greater
- **Skin cancer** 1.39X greater
- **Brain cancer** 1.31X greater
- **Prostate cancer** 1.28X greater
- **Colon cancer** 1.21X greater

(231-235)

INITIATIVES TO ADDRESS RISKS

In 2023, the CDC launched the **National Firefighter Registry for Cancer** (NFR) in collaboration with the National Institute for Occupational Safety and Health (NIOSH) in response to the Firefighter Cancer Registry Act passed in 2018 by Congress. This registry is the **largest effort undertaken so far to understand cancer burden among U.S. firefighters**. The NFR expands upon previous registries by including more women, diverse racial and ethnic groups, and volunteer firefighters, making the data more inclusive and representative. These data will pave the way for new health and safety measures for firefighters to protect them from developing cancer.

Be Cognizant of Hormonal Factors

Pregnancy and Breastfeeding

Historically, parous women – women who have given birth – were known to be less likely to develop breast cancer than nulliparous women – women who have never given birth. This protective effect of pregnancy reduces the risk of developing a type of breast cancer called estrogen receptor-positive tumor (242-244). Importantly, the risk reduction is only manifested after a decade or longer following a woman's last pregnancy, with greater protection conferred with increasing time (242-244). Parous women are at reduced risk for developing breast cancer after menopause (when most breast cancers are diagnosed) compared to their nulliparous peers.

In contrast, between five to ten years after giving birth, known as the postpartum period, women face a short-term, elevated risk for a different type of breast cancer called estrogen receptor-negative tumors compared to women who have never given birth (245). Finally, young women are at a higher risk of developing triple-

Women can reduce their risk of developing breast cancer by 4.3 percent for every 12 months of breastfeeding. This is in addition to the seven percent decrease observed for each birth (257).

negative breast cancer; the risk is elevated in the postpartum period but decreases over time (242,244,245). Identifying interventions that may alleviate the tumor-promoting potential of recent childbirth, and determining the best therapeutic options to treat postpartum breast cancer, are areas of extensive investigation.

There is evidence that breastfeeding can be protective against the development of estrogen receptor-negative breast cancer in mothers that is associated with giving birth (246-248), with increased duration of breastfeeding associated with further decrease in risk (160,244,247,249-251). Emerging data suggest that breastfeeding may also be associated with a lower risk of ovarian cancer development (252,253). The protective effects of breastfeeding are seen in both Black and White women (160,247,249,250). Notably, the increased risk of triple-negative breast cancer diagnosis associated with giving birth can be reduced by breastfeeding, with longer durations of breastfeeding further decreasing the risk (160,244,246,249,250,254). Beyond protecting the mother, emerging data suggest that breastfeeding can also reduce the risk of children developing leukemia. The protective effect increased proportionally with duration of breastfeeding (255,256).

While breastfeeding is not always an option, the awareness of the benefits of breastfeeding in reducing cancer risk is low among U.S. women (258). Culturally tailored public education and implementation of health policies in support of lactation are needed, specifically for medically underserved populations, such as young Black women, who have a lower prevalence of breastfeeding and a higher incidence of aggressive breast cancers compared to all other U.S. racial and ethnic groups (259,260).

Hormone Replacement Therapy

Hormone replacement therapy (HRT) refers to treatments that aim to relieve the common symptoms of menopause and the long-term biological changes, such as bone loss, that take place after menopause. These changes occur due to the decline in the levels of the hormones estrogen and progesterone. Hormone replacement therapy usually involves treatment with estrogen and progestin or estrogen alone in women who have undergone a hysterectomy. This is because when estrogen is given alone, but not in combination with progestin, it is associated with an increased risk of endometrial cancer, a type of cancer that forms in the tissue lining of the uterus.

Data show that women who use the estrogen and progestin combination have an increased risk of developing breast cancer (261,262). The risk is greater with longer duration of use and is nearly two-fold higher among women who have used estrogen and progestin in combination for 10 years or longer compared to those who never used HRT (263-265). Women who are no longer using HRT have a lower risk than current users but remain at an elevated risk for more than a decade after they have stopped taking the drugs (264). Individuals who seek HRT should discuss with their health care providers the advantages and possible risks, before deciding what is right for them.

One area of ongoing investigation in exogenous hormone use is the differential cancer risks among individuals undergoing gender-affirming hormonal therapy (266). While current data are very limited, there is emerging evidence indicating an increased risk of breast cancer but a lower risk of prostate cancer among trans women who received gender-affirming hormonal therapy compared to age-matched cisgender men. Trans men who received gender affirming hormonal therapy had a lower risk of breast cancer compared to age-matched cisgender women (267,268). New evidence indicates that this lower risk of breast cancer in trans men may be due to protective effects of receiving androgen therapy during their transition (269). Long-term, population-based studies are needed to comprehensively assess the risk of cancers in these understudied and medically underserved populations.

Screening for Early Detection

IN THIS SECTION, YOU WILL LEARN:

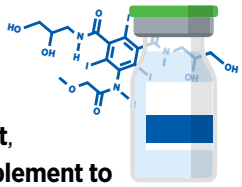
- Screening for cancer means looking for cancer or abnormal cells that may become cancer in people who do not have any signs of the disease.
- In the United States, independent panels of experts, convened by the government or by professional organizations, carefully evaluate the benefits and harms of cancer screening tests before issuing screening recommendations.
- Extensive research has shown that routine cancer screening saves lives.
- Advances in medical research are underscoring the potential for artificial intelligence and minimally invasive screening tests as new frontiers in early detection of cancer.
- Additional research is needed for early detection of certain cancer types, such as cancers of the ovary, pancreas, and liver, that have high mortality rates but no population-level screening tests.
- Evidence-based interventions can increase adherence to recommended screening guidelines but disparities in the uptake of cancer screening persist.

Cancer screening means checking for cancer, or for abnormal cells that may become cancerous, in people who have no signs or symptoms of the disease. Screening for cancer according to evidence-based guidelines can help find aberrations at the earliest possible detectable phase during cancer development and progression. Health care providers use the information gleaned from a cancer screening test to make an informed decision on whether to monitor or treat, or surgically remove, precancerous lesions or early-stage cancer before they progress to a more advanced stage (see **Figure 10**, p. 55).

There are different kinds of cancer screening tests that include laboratory tests to determine the changes in cancer biomarkers in biospecimen samples, and imaging or endoscopic procedures to look for specific abnormalities. In the United States, the U.S. Preventive Services Task Force (USPSTF), an independent Congressionally-mandated panel of experts in preventive care, rigorously reviews the evidence on the benefits and harms of behavioral counseling, preventive medications, and screening strategies related to cancer (see **Sidebar 18**, p. 56).

A recent study of more than one million women found that **digital breast tomosynthesis** had a **higher rate of breast cancer detection** and a **lower rate of false positives** compared to standard digital mammography alone (273).

In June 2023, **FDA approved** iopromide-300 and -370 (Ultravist), an **iodine-based contrast agent**, which can be **used as a supplement to mammography and/or ultrasound** for enhanced visualization of known or suspected lesions of the breast in adults (270, 271).



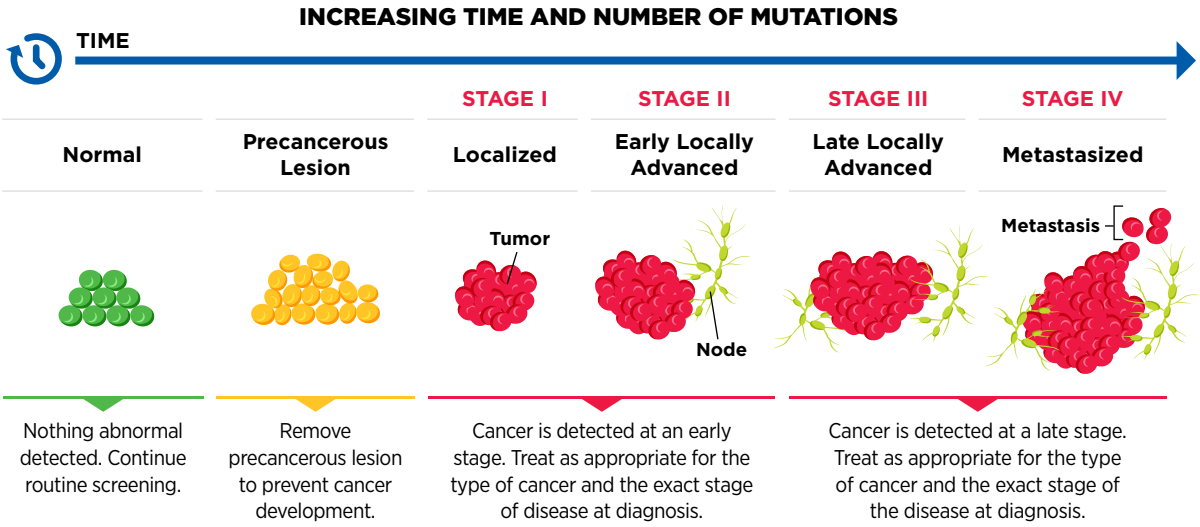
There are other tests beyond those recommended by the USPSTF that are also used by clinicians for detecting cancer. As one example, magnetic resonance imaging (MRI) is not a USPSTF-recommended test, and is not typically used to screen for breast cancer. However, a breast MRI may be performed to further evaluate abnormal findings on mammograms for persons with dense breast tissue, which makes it hard to see abnormal areas on mammography (272). Researchers also continually evaluate the safety and accuracy of new and improved methods.

Importance of Cancer Screening

The overarching goal of cancer screening is to reduce the burden of cancer in the general population. Guidelines and

FIGURE 10

What Can Cancer Screening Find and What Can Be Done?



When a person undergoes cancer screening, the test result could be negative, positive, indeterminate, or incomplete. When the screening test does not indicate an abnormality, the person should continue routine screening in close consultation with a clinician as long as the benefits of routine cancer screening for the individual continue to outweigh potential harms.

If the test detects a precancerous lesion, the lesion can be treated, thus minimizing the likelihood of its progression into cancer. If the test finds a cancer at an early stage of development, for example, stage I or stage II for a solid tumor, the patient can be treated successfully and has a higher likelihood of a cure.

Treatment is less likely to be curative if cancer is detected at a later stage of development, i.e., stage III or stage IV.

Treating a precancerous lesion or cancer at the earliest stage of development is called cancer interception, which is an area of active research for its potential to minimize the burden of cancer.

Adapted from (1).

recommendations have been created to help individuals and their health care providers decide together whether an individual should be screened for cancer, at what age the screening should start, how frequently the screening should be done and by which method, and if and at what age the screening should stop.

Routine screening aims to catch precancerous lesions or cancer at an early stage when they can be treated more effectively, thus reducing cancer-related deaths (see **Figure 10**, p. 55) (274). Accruing evidence suggests that recommended cancer screening lowers cancer mortality. In a recent study, researchers analyzed the rate of lung cancer-related mortality from eight clinical trials comprising more than 90,000 participants who received lung cancer screening using either the low-dose computed tomography (LDCT) or chest radiography, or who did not receive lung cancer screening (275). Findings showed a 21 percent reduction in lung cancer-related deaths in participants who were screened for lung cancer using LDCT, compared to the other two groups. Despite the evidence of the benefits, uptake of the recommended lung cancer screening remains suboptimal among eligible individuals (see **Sidebar 22**, p. 63).

It is equally vital to receive follow-up testing if the screening test is abnormal, which may indicate the presence of precancerous lesions or cancer. There is strong evidence that many people do not receive follow-up testing after a positive screening test (see **Sidebar 22**, p. 63).

One study examined data from more than 32,000 average-risk individuals who had received a positive result from stool-based screening for colorectal cancer between 2017 and 2020. Researchers found that only 53.4 percent received follow-up colonoscopy within one year of receiving the positive result from the initial screening test (276). This is unfortunate considering recent data, which show that not receiving the follow-up colonoscopy after a positive stool-based test doubles the risk of dying from colorectal cancer (277). A modeling study estimated a 16 to 23 percent reduction in colorectal cancer-related deaths among individuals who followed up with colonoscopy after a positive stool-based test (278). These findings highlight the importance of receiving follow-up testing after an abnormal screening test.

SIDEBAR 18

USPSTF-recommended Tests to Screen for Cancer

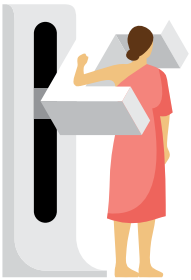
The U.S. Preventive Services Task Force (USPSTF) is an independent Congressionally mandated panel of experts in preventive care convened by the Agency for Healthcare Research and Quality. USPSTF rigorously reviews the evidence on the benefits and harms of behavioral counseling, preventive medications, and screening strategies related to cancer (see **Figure 11**, p. 58).

Described below are screening tests that are included as part of evidence-based recommendations by USPSTF to screen for four cancer types in individuals who are at an average risk of being diagnosed with cancer, and to screen for lung cancer in individuals who are at a higher-than-average risk of being diagnosed with cancer.

BREAST CANCER

Digital mammography

Uses X-rays to generate two dimensional images of the breast that can be stored electronically and analyzed for signs of breast cancer.



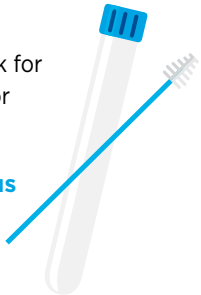
Digital breast tomosynthesis

Also called three-dimensional mammography, this screening method generates 3D images of the breast that are analyzed for signs of breast cancer. Must be accompanied by digital mammography.

CERVICAL CANCER

Cytology

Samples cervical cells, which are analyzed under a microscope to look for abnormalities. Also called Pap test or Pap smear.



High-risk Human Papillomavirus (HPV) test

Detects the presence of certain cervical cancer-causing types of HPV and identifies people for whom further testing is recommended. Does not directly detect precancerous or cancerous cervical lesions.

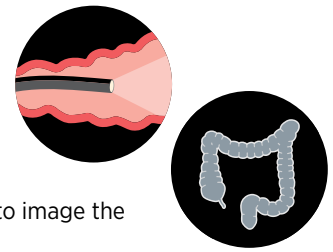
COLORECTAL CANCER

Stool-based tests

Some test for the presence of a product of red blood cells. Others test for both the presence of a product of red blood cell and certain genetic mutations linked to colorectal cancer. Do not directly detect precancerous lesions or cancers but identify people for whom further testing is recommended.

Direct visualization tests

Flexible sigmoidoscopy and colonoscopy Use a thin, flexible, lighted tube with a small video camera on the end to examine the lining of the entire colon and rectum (as is the case with colonoscopy), or only certain parts (as is the case with flexible sigmoidoscopy).

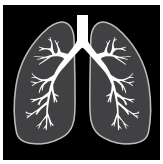


Computed tomography (CT) colonography (virtual colonoscopy) Uses X-rays to image the colon and rectum.

LUNG CANCER

Low-dose spiral CT scan

Uses low doses of X-rays to rapidly image the lungs and detect any structural abnormalities suggestive of lung cancer. Suspicious lesions are then biopsied to examine for the presence of abnormal or cancer cells.



PROSTATE CANCER

PSA test

Measures the level of a protein called prostate-specific antigen (PSA) in blood, which is often elevated in men with prostate cancer. Does not directly detect prostate cancer but identifies men for whom further testing is recommended.

Adapted from (1).

SIDEBAR 19

Benefits and Potential Harms of Cancer Screening

The U.S. Preventive Services Task Force (USPSTF) or other professional societies focused on cancer care meticulously review the available scientific evidence to weigh benefits of screening for a specific cancer type against potential harms before issuing final screening guidelines. Because no individual test is perfect, USPSTF recommendations include a letter grade; screening tests that are recommended with a Grade A or B have been shown to have benefits that outweigh potential harms from screening (see **Sidebar 20**, p. 59).

It is important to note that harms from a cancer screening test are rare. Furthermore, the benefits-to-potential-harms ratio can vary for different population groups as well as for individuals based on age, gender, and existing medical conditions among other factors.

BENEFITS

Reduced cancer mortality

If a screening test detects precancerous lesions or cancer at an early stage of development, it may increase the likelihood that a patient can be successfully treated, thus reducing the risk of dying from cancer.

Reduced cancer incidence

If a screening test detects precancerous lesions, removing these lesions can reduce, or even eliminate, an individual's risk of ever developing the screened cancer.

Reduced likelihood of advanced disease

If a screening test detects cancer at an early stage of development, it may reduce an individual's risk of being diagnosed with the screened cancer at an advanced stage, thus making treatment more successful and avoiding more complex treatment regimens.

POTENTIAL HARMS

Adverse events

Screening tests could carry risks of harm. For example, colonoscopy can potentially cause a cut in the wall of the colon in rare cases.

Anxiety

Screening tests could cause fear, worry, and/or anxiety in individuals who are eligible for cancer screening and may not have the disease.

False-negative test results

Screening tests could sporadically give negative results in individuals who are not free from the screened cancer, leading to missed opportunities for early treatment.

False-positive test results

Screening tests could give false-positive results in individuals who do not have the screened cancer, leading to additional unnecessary medical procedures, treatments, and anxiety.

Overdiagnosis and overtreatment

Screening tests could sometimes overdiagnose, i.e., detect precancerous lesions or cancers that may not go on to cause symptoms and threaten life, leading to overtreatment with its own potential harms.

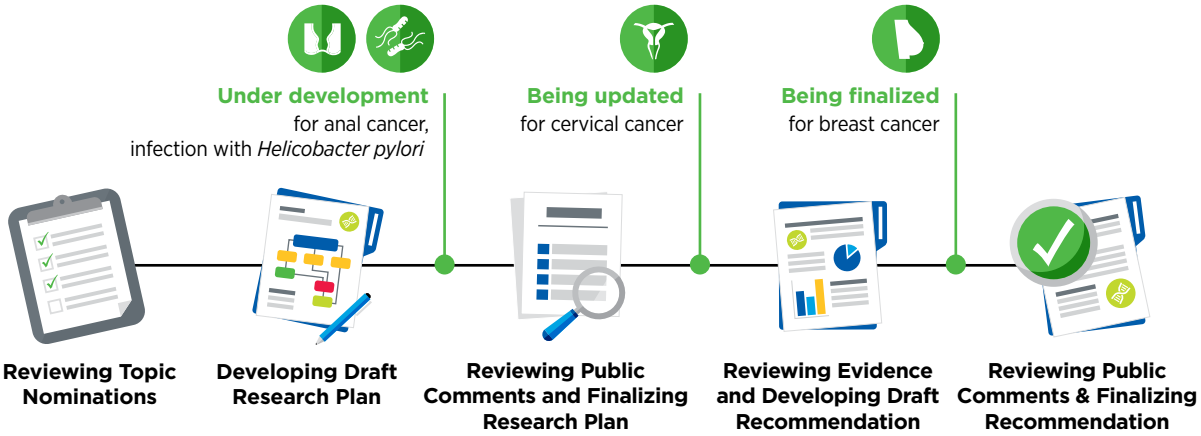
Incidental findings

Screening tests might find an unrelated medical issue—such as finding an unrelated heart problem—and require follow-up tests or procedures which also have risks.

Although risks and benefits of cancer screening tests are carefully considered during the development of screening recommendations, it is important to note that screening tests are medical procedures and carry potential harms. It is thus concerning that a recent study found that not all cancer screening recommendations and guidelines included potential harms associated with screening tests. Researchers reviewed 33 commonly used screening guidelines from various expert panels and found that some harms were not mentioned at all, while others were mentioned only briefly (279). It is vital that the information about benefits and potential harms of cancer screening is clearly and easily available so that people can make an informed and shared decision in consultation with their health care providers (see **Sidebar 19**, p. 57).

FIGURE 11

The Process Used by the U.S. Preventive Services Task Force to Develop Cancer Screening Guidelines



Developing guidelines for cancer screening is a multistep process. Panels of subject matter experts, such as those who make up the U.S. Preventive Services Task Force (USPSTF), meticulously review the available evidence and carefully weigh benefits of cancer screening against any potential harms before recommending if and at what age and risk level a person should start or stop cancer screening, for which cancer type, how frequently, and by which method.

In the multistep process used by USPSTF for developing screening guidelines, anyone can nominate a new topic for review at any time. USPSTF reviews, selects, and prioritizes nominated topics based on relevance to and impact on disease prevention, primary care, and public health. USPSTF develops a research plan and posts a draft research plan on its website for public comments. USPSTF and Evidence-based Practice Center (EPC) review public comments and revise the research plan as needed. USPSTF posts the final research plan on its website.

USPSTF assesses EPC-gathered evidence, weighing effectiveness and benefits/harms, and develops a draft recommendation statement, which is posted on the website, along with EPC evidence review, for public comments. Both the draft recommendation and evidence review are revised and finalized based on public comments and published in a journal and on the USPSTF website.

Indicated in green are cancer types for which USPSTF is at various stage of developing screening recommendations. There are some differences in the process used by different organizations, but all organizations aim for the same rigor to ensure maximal benefit and minimal harm to public health.

Developed from (4).

Guidelines for Cancer Screening

In the United States, guidelines for cancer screening are carefully developed by groups of subject matter experts and professional societies. For example, an independent group of experts convened by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services carefully evaluates data regarding the benefits and potential harms of different approaches to disease prevention, including cancer screening tests, genetic testing, and preventive therapeutics, to make evidence-based recommendations about the use of these in primary care settings. These volunteer experts form the U.S. Preventive Services Task Force (USPSTF).

During the development of cancer screening recommendations, USPSTF is supported by researchers from the Evidence-based Practice Center (EPC) program, a U.S. Agency for Healthcare Research and Quality initiative (see **Figure 11**, p. 58).

When developing cancer screening guidelines, subject matter experts such as those who make up USPSTF consider gender and age, as well as additional characteristics that are specific to individuals or population groups for whom the screening guidelines are being developed. These considerations include whether or not a person has a particular organ (e.g., for cervical cancer screening, whether an individual never had a cervix or had a hysterectomy with cervix removal); has a smoking history (e.g., for lung cancer screening); has an all-negative prior screening history (e.g., for cervical cancer screening); has other health-related issues that may reduce life expectancy (e.g., for

SIDEBAR 20

The USPSTF Grading System for Cancer Screening Guidelines*

Below are simplified definitions of the grades the U.S. Preventive Services Task Force (USPSTF) assigns to its cancer screening recommendations:

GRADE	RECOMMENDATION	REASON
A	Screening recommended	High certainty that net benefit is substantial
B	Screening recommended	High certainty that net benefit is moderate
C	Selective screening recommended based on professional assessment and patient preference	Moderate certainty that net benefit is small
D	Screening not recommended	Moderate to high certainty that screening has no net benefit, or that the harms outweigh the benefits
I	Not applicable	Insufficient evidence to assess the balance of benefits and harms of screening

*Definitions included here are based on grade definitions after July 2012. A complete description for each grade, and the definitions for the guidelines issued before July 2012, can be accessed at the USPSTF website (280).

prostate cancer screening); and/or has a family history of cancer (e.g., for colorectal and breast cancer screening).

For the finalized guidelines, USPSTF assigns a grade to its recommendations (see **Sidebar 20**, p. 59). The grade of evidence also informs which services are covered without out-of-pocket costs under the Affordable Care Act. The USPSTF can assign different grades to different population groups within the same cancer type. For example, a Grade A recommendation is assigned for adults ages 50 to 75 and a Grade B for adults ages 45 to 49 to screen for colorectal cancer.

USPSTF guidance for cancer screening includes recommending for screening certain individuals at certain intervals (see **Sidebar 21**, p. 60); recommending against screening that has been shown to be harmful; and deciding that there is insufficient evidence to make a recommendation. For example, USPSTF recently concluded that there is insufficient current evidence to support visual skin examination as a basis to screen average-risk adolescents and adults for skin cancer (281).

Eligibility for Cancer Screening

Cancer screening guidelines are developed for individuals who are at an average risk of being diagnosed with cancer, as well as for those who are at a higher-than-average risk of being diagnosed with cancer.

Key considerations that determine who should receive cancer screening and for which cancer include gender and age. Additional factors considered for cancer screening include genetic, environmental, behavioral, and social influences. Because some of these factors are different for each person and may change throughout life, the eligibility of an individual for cancer screening may also change over time. The decision of whether someone should receive cancer screening is different for each person.

Researchers are also continually evaluating accruing evidence to recommend changes to existing eligibility criteria to screen for different types of cancer. For example, studies have found that even if all those who are eligible for lung cancer screening under the current USPSTF-recommended guidelines were to undergo screening, a large proportion of lung cancers will still be missed (282). One study of nearly 2000 patients with lung cancer found that only 54 percent of patients would have been deemed eligible for screening under the current USPSTF recommendations (283). As more evidence accumulates indicating that existing recommendations need to be revised, USPSTF and other cancer-focused organizations reevaluate existing screening recommendations and make evidence-based adjustments.

It is important that people empower themselves with the most up-to-date information on cancer screening eligibility by having

SIDEBAR 21

USPSTF Guidelines for Cancer Screening*

The U.S. Preventive Services Task Force (USPSTF) carefully reviews available data and weighs the risks and benefits for the general population before issuing cancer screening guidelines (see **Figure 11**, p. 58). Currently, USPSTF has guidelines for five types of cancer, four of which apply to individuals who are at an average risk of being diagnosed with breast, colorectal, prostate, or cervical cancer. Guidelines for lung cancer apply to those who smoked previously or who currently smoke; these individuals are at a higher-than-average risk of being diagnosed with the disease because of tobacco use.

BREAST CANCER**

The new draft recommends mammogram every other year for women ages 40 to 74.

CERVICAL CANCER**

Cervical cytology every three years for women ages 21 to 65; high-risk human papillomavirus testing alone, or in combination with cytology, every five years for women ages 30 to 65.

COLORECTAL CANCER

Stool-based tests every one to three years, and/or colonoscopy/flexible sigmoidoscopy every five to 10 years, for all adults ages 45 to 75.

LUNG CANCER†

Low-dose computed tomography every year for all adults ages 50 to 80 who are current smokers or who quit within the past 15 years, with a 20 pack-year smoking history.

PROSTATE CANCER

Periodic prostate-specific antigen-based test, by making a shared decision with health care provider through an ongoing dialogue, for men ages 55 to 69.

*Only USPSTF guidelines are included here. Several other professional societies issue evidence-based screening guidelines for certain types of cancer that may differ from those issued by USPSTF. Furthermore, guidelines have been simplified for brevity. Readers are advised to visit the USPSTF website (https://www.uspreventiveservicestaskforce.org/uspstf/) for a complete description of guidelines and more detailed information.

**USPSTF is currently in the process of updating the recommendations for breast and cervical cancer.

† Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

an ongoing dialogue with their health care providers and develop a personalized cancer screening plan that considers their specific risks and tolerance of potential harms from screening tests.

Those at an Average Risk of Being Diagnosed with Cancer

Individuals at average risk of being diagnosed with cancer are those who do not have a family history of cancer or personal history of cancer, and do not have an inherited genetic condition that places them at a higher risk of developing cancer. Two key considerations for recommending screening in average-risk individuals are gender and age. USPSTF recommends that average-risk individuals should receive routine screening for breast, cervical, and colorectal cancer when they reach the eligible age (Grades A and/or B recommendations). For prostate cancer screening, USPSTF recommends that average-risk individuals should have an ongoing dialogue with their health care provider to make an informed and shared decision, when they reach the eligible age (Grade C) (see **Sidebar 21**, p. 60).

The probability of developing cancer increases with advanced age. According to the most recent estimates, 88 percent of people diagnosed with cancer in the U.S. are 50 or older (28). Therefore, researchers continually evaluate, among other factors, the optimal age for starting or stopping cancer screening, and expert panels, such as USPSTF, periodically update guidelines based on the new evidence.

As one example, in May 2023, USPSTF proposed reducing the recommended starting age of screening from 50 to 40 for women who are at an average risk of developing breast cancer. Researchers estimate that the new guidance could save 19 percent more lives from breast cancer (284). People should discuss cancer screening during routine consultations with their health care providers, and evaluate their cancer screening plans according to the most up-to-date information.

Those at a Higher-Than-Average Risk of Being Diagnosed with Cancer

Individuals at a higher-than-average risk of being diagnosed with cancer are those who have a strong family history of cancer, a personal history of cancer, certain tissue makeup, an inherited genetic condition, or are exposed to one or more cancer risk factors, all of which place them at a higher risk of developing cancer. One example is individuals who consume tobacco products. According to CDC, people who smoke cigarettes are 15 to 30 times more likely to develop lung cancer or die from it than people who do not smoke.

Women with extremely dense breast tissue are considered at higher-than-average risk of developing breast cancer compared to women with less dense breast tissue. Because of gaps in the current knowledge, USPSTF does not recommend additional screening tests for women with extremely dense breasts in the recently released draft statement of the revised recommendations for breast cancer screening (284). However, other cancer-focused organizations do recommend additional screening tests for women with dense breast tissue (285). Furthermore, 38 U.S. states currently require some level of breast density-related notification after a mammogram, and many provide expanded insurance coverage for additional screening for those who have dense breast tissue (286).

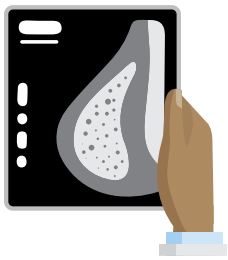
It is important to note that extremely dense breast tissue is only one of many risk factors for breast cancer. More research is necessary to determine why women with dense breast tissue are at a higher-than-average risk of being diagnosed with breast cancer and whether this knowledge can be used to improve risk prediction models for breast cancer.

Another group of individuals at higher-than-average risk of being diagnosed with cancer is people with inherited cancer susceptibility syndromes (or hereditary cancer syndromes), which are caused by genetic mutations that can be passed on from one generation to the next and can predispose an individual to develop certain types of cancer (see **Figure 5**, p. 31). For example, individuals who have Lynch syndrome, which is caused by mutations in genes important for repairing damaged DNA, have an increased risk of developing colorectal cancer, endometrial cancer, ovarian cancer, and many other types of cancer. USPSTF recommends that individuals with a personal or family history of Lynch syndrome should speak with their health care providers about appropriate screening options (288).

Individuals who consider themselves at a high risk for an inherited cancer-predisposing genetic mutation should, in consultation with their health care providers, also consider genetic counseling and testing. Expert panels sometimes issue guidelines for genetic counseling and testing. For example, in 2019, USPSTF issued recommendations for breast cancer risk assessment, genetic counseling and genetic testing for women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with *BRCA1/2* gene mutation (see **Figure 12**, p. 62) (289).

Genetic testing may aid individuals and their health care teams in deciding whether, increased frequency of breast cancer screening with MRI, preventive surgery (see **Supplemental Table 1**, p. 191), or chemoprevention (e.g., use of selective estrogen receptor modulators) would help reduce the risk of developing cancer later on in life. It is concerning that only 6.8 percent of more than 1.3 million people had undergone genetic testing, according to a recent study examining the extent of germline mutations among people diagnosed with cancer (290). It is imperative that individuals who are at a high risk for being diagnosed with cancer because of inherited mutations consult with their care team for whether or when they should undergo genetic testing.

WHAT IS DENSE BREAST TISSUE?



Density of the breast tissue in a mammogram is **determined by** the comparative **amounts of fibrous, glandular, and adipose tissues** that make up the breast. The higher the amount of fibrous and glandular tissue, the denser the breast tissue appears in the mammogram.

In March 2023, FDA issued updated guidance, requiring mammography facilities to notify patients about the density of their breasts (287).

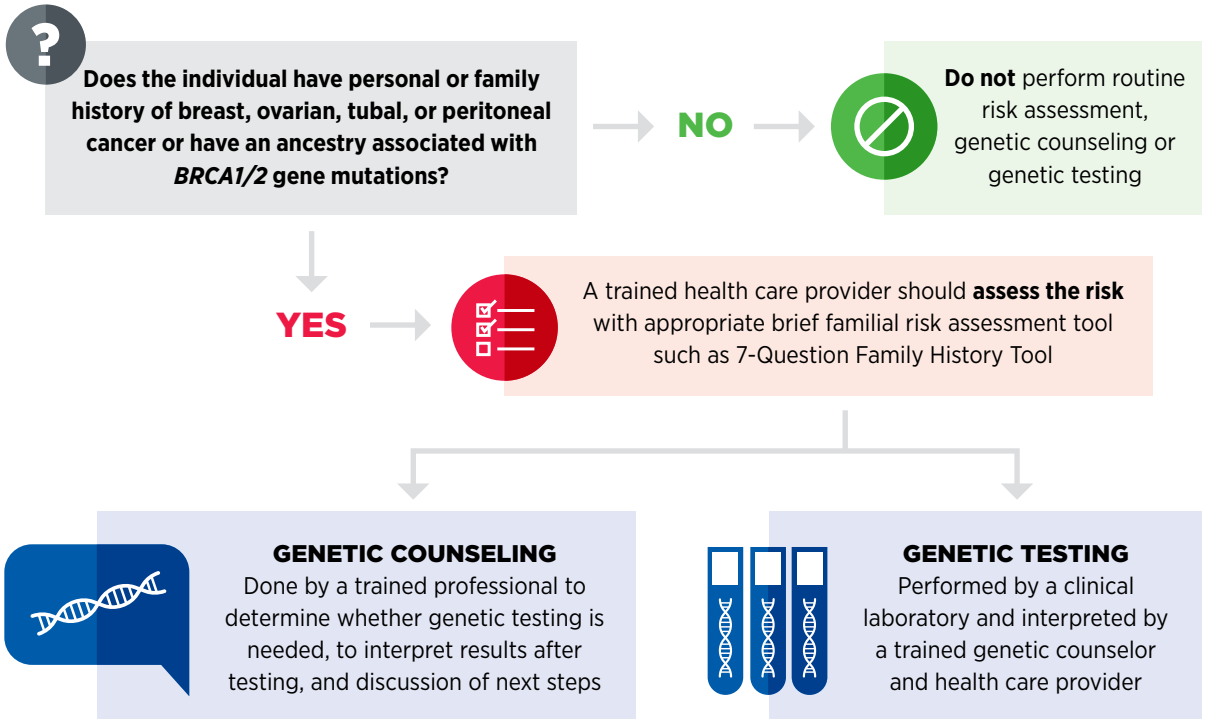
Suboptimal Uptake of Cancer Screening

Evidence shows that adherence to recommended cancer screening saves lives (see **Importance of Cancer Screening**, p. 54). In a recent study, researchers found that 80 percent of the study participants who received a diagnosis of lung cancer at an early stage via routine lung cancer screening were living 20 years after the initial diagnosis (291). Despite the benefit of lung cancer screening, unfortunately, only six percent of U.S. individuals eligible for lung cancer screening were up to date with the recommended screening in 2022 (236).

It is equally important to know when an individual should stop screening for cancer. USPSTF recommendations include the age

FIGURE 12

USPSTF Recommendation for Breast Cancer Genetic Testing in Women



USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with mutations in breast cancer 1 and 2 (*BRCA1/2*) genes with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.

past which the potential harms from screening tests are likely to outweigh benefits (see **Sidebar 20**, p. 59). For example, USPSTF guidelines recommend against screening for prostate cancer in men older than 69. However, a recent study found that 55.3 percent of men ages 70 to 74, 52.1 percent of men ages 75 to 79, and 39.4 percent of men age 80 and older were screened for prostate cancer in 2020 (292).

Suboptimal adherence to recommended cancer screening guidelines is evident across cancer types, and researchers are continually working to develop evidence-based approaches to increase adherence to cancer screening guidelines (see **Progress Toward Increasing Adherence to Cancer Screening Guidelines**, p. 64). The COVID-19 pandemic has further adversely impacted cancer screening rates (293). A recent study evaluating the impact of the COVID-19 pandemic on cancer screening found that, in the United States between 2019 and 2021, screening within a prior year decreased from 60 percent to 57 percent for breast cancer, from 45 percent to 39 percent for cervical cancer, and from 39.5 percent to 36 percent for prostate cancer (259).

Another area of major concern is the inequities in cancer screening and follow-up testing among certain U.S. population groups (see **Sidebar 2**, p. 17). For example, compared to the overall U.S. population, cancer screening rates are lower among certain racial and ethnic as well as sexual and gender minorities (see **Sidebar 22**, p. 63) (293). A multitude of barriers contribute to low screening rates, including social and structural barriers; bias and discrimination against minorities in the health care system; mistrust of health care professionals among minorities; lack of access to quality health insurance and coverage; low health literacy; and miscommunication between patients and providers (13).

It is important to fully understand why individuals belonging to certain population groups are at a higher risk of being diagnosed with certain types of cancer, and whether suboptimal uptake of screening contributes to this higher risk. Furthermore, there is an urgent need to collect disaggregated data related to all aspects of cancer burden and clinical care from individuals belonging to racial and ethnic minorities, sexual and gender minorities, and others who are socially and economically disadvantaged, including people who belong to

SIDEBAR 22

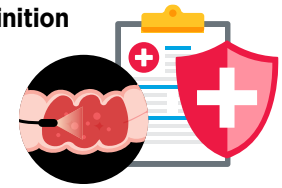
Inequities in Cancer Screening

Racial and ethnic minorities and other populations that are medically underserved experience disparities in cancer screening uptake, as well as in receiving follow-up testing when the initial cancer screening test shows an abnormality. Examples presented here highlight inequities in cancer screening and follow-up testing as documented in recent studies:

28%* less likely	**Residents of the most socially vulnerable U.S. counties**—areas that are adversely affected by natural disasters (e.g., disease outbreak) or socioeconomic deprivation (e.g., poverty)—were 28 percent **less likely to receive colorectal cancer screening** compared to those living in the least socially vulnerable U.S. counties (295).
25% less likely	**Hispanic individuals** were 25 percent **less likely to receive colorectal cancer screening** compared to NHW individuals (296).
27.5% less likely	**Individuals living in Midwestern states** were 27.5 percent **less likely to receive LDCT for lung cancer screening** compared to those living in the Northeastern states (297).
36% vs 22%	Thirty-six percent of **Asian women ages 21 to 65 did not receive cervical cancer screening** compared to 22 percent of White women in the same age group (298).
Only 50%	**Only 50 percent** of **transgender individuals** had received **breast cancer screening** and **only 47 percent** had received **cervical cancer screening** within the past five years, based on a recent survey (299).
51% vs 3%	Nearly 51 percent of **women living in rural areas** had **limited access to mammography** for breast cancer screening compared to just three percent of those living in urban areas (300).
44% less likely	**Black individuals** were 44 percent **less likely to have received lung cancer screening** compared to White individuals (301).

*All values in this sidebar are rounded to the nearest integer.
LDCT, low-dose computed tomography; NHW, non-Hispanic White

In February 2023, the Centers for Medicare & Medicaid Services expanded the **definition of colorectal cancer screening to also cover a follow-up colonoscopy**. Previously, individuals had to pay 20 percent out-of-pocket cost toward a follow-up test if an initial stool-based test returned a positive result (294). **The change has the potential to reduce inequities in colorectal cancer screening.**



more than one of these populations, as detailed in the *AACR Cancer Disparities Progress Report 2022* (13). Evidence gathered from such data will help with developing cancer care guidelines and interventions to improve care delivery that is tailored to specific populations, which may lead to health equity for all.

SIDEBAR 23

Evidence-based Interventions to Increase Adherence to Cancer Screening

According to the Centers for Disease Control and Prevention (CDC), evidence-based interventions are strategies that improve delivery of cancer screening and increase the number of people screened.

Below are recent examples of some of the evidence-based interventions that have been shown to increase cancer screening adherence among eligible individuals:

Combining tailored educational material with patient navigation

An interactive video of tailored messages about cancer screening followed by a phone call with a patient navigator **increased adherence to routine screening for breast, cervical, and colorectal cancers** six times among women living in rural areas (305).

Mailing self-collection sample kits

Mailing human papillomavirus self-collection kits to women eligible for cervical cancer screening **nearly doubled the screening uptake** (306).

Using digital interventions

Using telemedicine as well as Internet- and mobile device-based technologies to help make informed decisions resulted in a **1.5 times increase in the completion rate for colorectal cancer screening** (307).

Implementing public health campaigns

Clinics that participated in the Colorectal Cancer Control Program of CDC and applied a combination of three or more evidence-based interventions increased the uptake of colorectal cancer screening by five percentage points (308).

Progress Toward Increasing Adherence to Cancer Screening Guidelines

Multilevel and multipronged approaches are required to eliminate cancer health inequities across the continuum of care, including uptake and follow-up of recommended evidence-based cancer screening among all eligible individuals (see **Sidebar 23**, p. 64). Stakeholders across the cancer care continuum (see **Sidebar 1**, p. 13) are working together to achieve these goals.

In the United States, the Community Preventive Services Task Force (CPSTF), established by the U.S. Department of Health and Human Services in 1996 at CDC, develops guidance on community-based health promotion and disease prevention. Based on the available scientific evidence, CPSTF periodically issues recommendations and findings on public health interventions designed to improve health and safety. As one example, CPSTF recently reviewed 34 studies evaluating the effectiveness of patient navigation in increasing cancer screening uptake among racial and ethnic minority populations and people with lower incomes (303). Based on the findings, CPSTF recommended in the *2022 Annual Report to Congress* that patient navigation services should be provided to medically underserved communities to increase breast, cervical, and colorectal cancer screening (304). The Task Force concluded that patient navigation services advance health equity. Patient navigation also improves timely and appropriate follow-up care and treatment, and may improve health and reduce cancer-related disparities for the racial and ethnic populations and people with lower incomes who are medically underserved.

> Only 28 percent of physicians surveyed
> reported having **received training** regarding **cancer screening** for patients belonging to **sexual and gender minorities** (302).

Recognizing the critical importance of regular cancer screening in saving lives, the National Cancer Plan, released by NCI in April 2023, prioritizes early cancer detection and cancer prevention (309). The plan calls for new technologies and

methods to detect cancers early, especially cancers for which no screening tests exist currently (such as cancers of the liver and pancreas), and to eliminate precancerous lesions before they become cancerous while minimizing side effects.

New Frontiers in Cancer Screening

Researchers are working on novel methods and strategies that may improve detection of early cancers and/or precancerous lesions to reduce the death rate from cancer, while minimizing any potential harm from the procedure. Two areas of research with exciting new developments are the use of artificial intelligence and blood-based tests to detect cancer early.

Realizing the Potential of Artificial Intelligence for Early Detection of Cancers

There have been unprecedented advances in recent years in the use of artificial intelligence (AI) and machine learning (ML) in medicine, including for cancer detection. One of the several ways researchers are using AI and ML for cancer detection is in analyzing large amounts of imaging data collected for the purposes of cancer screening to recognize patterns that are otherwise time-consuming and difficult to discern by eye even by trained health care professionals (see **Sidebar 24**, p. 66).

A recent study found that AI-assisted colonoscopy detected 21 percent more polyps (clumps of usually benign cells that build up on the lining of the colon and can be precursors to colon cancer) compared to a conventional expert-directed colonoscopy (310). Another study described the development of a deep learning model that can predict future risk of developing lung cancer within the next one to six years following a single LDCT scan (311). It is important to note that applying AI in medicine is an area of active research and not all studies have found AI-assisted improvements in cancer detection (312). Additional research is needed to understand the benefit of AI-driven applications in cancer medicine and whether AI mitigates or worsens health disparities.

Some of the AI-driven medical devices and software have proven to be highly accurate in clinical trials when compared to current standard practices. In recent years, the number of FDA-approved AI-enhanced software systems for use in medicine, including early detection, has increased significantly (315). Here, we are using two recent examples—ProstatID and SKOUT—to highlight the progress in this exciting area of cancer research.

In July 2022, FDA approved ProstatID, which uses AI to measure the volume of the prostate gland from scans obtained using traditional MRI and detect suspicious cancerous lesions. ProstatID is approved for use in a health care facility or hospital to assist trained radiologists in the detection and characterization of potentially cancerous lesions using MRI data. The approval was, in part, based on two clinical studies showing improved detection of prostate cancer and fewer false positives when radiologists used ProstatID.

In September 2022, FDA approved SKOUT, a medical device that uses advanced computer vision technology designed to recognize polyps and suspicious tissue and provide real-time feedback to clinicians during colonoscopy. The approval was based on results from a large clinical study showing that detection of polyps and suspicious lesions was substantially improved when colonoscopy was aided with SKOUT compared to standard colonoscopy without the aid of SKOUT (719 versus 562 detections, respectively). The improved detection was even more pronounced for smaller polyps (44 percent increase when using SKOUT versus 29 percent increase when using standard colonoscopy) (313).

Examples of recent FDA approvals discussed here underscore the potential applications of AI in the clinic to aid early detection and diagnostic purposes. Uses of AI in other aspects of cancer care—genomic characterization of tumors, drug discovery, and improved cancer surveillance—are also active areas of research (see **Artificial Intelligence**, p. 146) (316).

Moving Toward Minimally Invasive Cancer Screening

Most cancer screening tests in current use are designed to detect only one type of cancer. Some of the tests are invasive medical procedures, with potential health risks (see **Sidebar 19**, p. 57). Researchers are actively working to develop ways to detect cancer using tests that are less invasive and safer. Liquid biopsy is one such way in which a sample of blood, urine, or other body fluid is used to look for signs of cancer.

Thanks to research, the knowledge that precancerous lesions and tumors shed a variety of materials (such as cancer cells and small pieces of DNA, RNA, or proteins) has led to the development of tests that can detect these materials in blood, urine, or other body fluids. Liquid biopsy approaches are already in routine use for making treatment decisions and/or monitoring if cancer has returned in patients who have already received cancer treatment, and can be especially beneficial for pediatric patients with cancer (317,318).

Liquid biopsy procedures can detect abnormal cells and/or other materials from tumors that are circulating in the blood. It is critical that liquid biopsy tests are highly specific in detecting cancer-derived changes that are absent in healthy cells before these

SIDEBAR 24

Artificial Intelligence in Early Cancer Detection

ARTIFICIAL INTELLIGENCE

The ability of a computer to perform tasks commonly associated with human intelligence, such as how to act, reason, and learn.

MACHINE LEARNING

A type of AI that is programmed to learn over time from the data provided to make predictions or decisions; the more comprehensive and inclusive data provided to an ML model, the better it will perform.

DEEP LEARNING

A type of ML that learns from huge amounts of data using complex algorithms, called artificial neural networks, that are modeled after how the human brain processes information.

BENEFITS

Potential benefits of AI-based approaches in early detection are **speed and accuracy** to detect existing cancers or to rule out that cancer is present. This may allow for better surveillance and intervention if/when needed. Two of the most common AI-enhanced approaches for cancer early detection and diagnosis include:

- **Detecting and classifying cancerous tumors** using various scans from radiological or pathological imaging.
- Combining conventional blood tests as well as liquid biopsies with AI-powered analyses for **cancer diagnosis**.

POTENTIAL DRAWBACKS

- The **lack of large, well-annotated cancer datasets** that are representative of the diversity of the population as well as of the distinct cancer burdens of various population groups is a significant barrier for the use of AI in cancer research and patient care.
- Because the use of AI in medicine is a newer technological advance, there may be **concerns among patients about the use of their clinical information**, including images and tissues.
- The use of AI in early detection and diagnosis of cancer is **still in its infancy**; inequitable use of AI may exacerbate disparities. All stakeholders must work together to ensure that the evidence is developed to show the benefit beyond detection alone, potential biases are minimized, and, when proven, there is equitable access of this technological advance.

SELECTED EXAMPLES OF AI-BASED DEVICES AND SOFTWARE IN CANCER DETECTION

JULY 2022

ProstatID

Approved by FDA in July 2022, is an AI-based software that uses AI to **measure the volume of the prostate gland** from images of the prostate and **detect suspicious cancerous lesions** in scans obtained using traditional magnetic resonance imaging.

SEPTEMBER 2022

SKOUT

Approved by FDA in September 2022, is a medical device that uses advanced computer vision technology designed to **recognize polyps and abnormal tissue** and **provide real-time feedback** to gastroenterologists during colonoscopy (313).

Developed from (314).

tests can be recommended for cancer screening in the general population (319). Ongoing efforts are focused on developing strategies to ensure that liquid biopsy tests are specific in detecting cancer(s) without compromising sensitivity of the test (320).

An exciting aspect of liquid biopsy tests is the possibility of screening for many cancer types simultaneously and potentially with high specificity. If these procedures, called multicancer detection (MCDs) assays or multicancer early detection tests, are found to be effective, they may make receiving cancer screening easier for individuals. These tests may also decrease potential physical harm(s) from some of the conventional cancer screening tests, such as colonoscopy. Furthermore, a minimally invasive test that can be used to screen for multiple cancer types could transform early detection of cancers; potentially increase participation in cancer screening; and may decrease some current barriers to cancer screening.

An ongoing study is evaluating the specificity and accuracy of an MCD test for more than 50 types of cancer. Findings thus far show that the test correctly identified two out of every three cancers in more than 5,000 people who had visited their health care providers with suspected symptoms. The test also correctly identified the site from which cancer originated in 85 percent of those cases (321). A recent modeling study using the cancer mortality data from England estimated that using MCDs would result in 17 percent fewer deaths from cancer per year (322).

It is important to note that the research evaluating the safety and efficacy of MCD tests for routine cancer screening is at an early stage. While the initial studies are encouraging, currently there are limited data from prospective clinical studies (319,320). Key issues that remain unresolved include whether MCD tests can detect early stages of multiple cancer types accurately; what will be the rate of false positive results; whether using an MCD test will provide benefits that outweigh potential harms; and how much these tests will cost. Large ongoing studies, such as NCI's Vanguard Trial, will answer some of these critically important questions.

THE NATIONAL CANCER INSTITUTE'S (NCI) RESEARCH INITIATIVES TO ACCELERATE PROGRESS IN LIQUID BIOPSY AND MULTICANCER DETECTION APPROACHES

- **The Precompetitive Collaboration on Liquid Biopsy for Early-Cancer Assessment** initiative is an academic-industrial partnership program, with the primary goal to address some of the existing challenges and to accelerate progress toward using liquid biopsy approaches for early cancer detection (323).
- **NCI's Vanguard Trial** is a large feasibility clinical study that will launch in 2024 and will recruit 24,000 participants to evaluate potential ways MCDs should be studied to determine whether or not they can be effective in screening for cancer (324).

Advancing the Frontiers of Cancer Science and Medicine

IN THIS SECTION, YOU WILL LEARN:

- Researchers are harnessing the knowledge of the cellular and molecular underpinnings of cancer initiation and progression to develop safer and more effective treatments for cancer.
- Advances in novel and innovative approaches to surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—the five pillars of cancer treatment—are saving and improving lives.
- From August 1, 2022, to July 31, 2023, FDA has approved 14 new anticancer therapeutics and two new imaging agents and has expanded the use of 12 previously approved anticancer therapeutics to treat additional cancer types.
- Included in the FDA approvals are the first antibody–drug conjugate for the treatment of ovarian cancer, several new molecularly targeted therapeutics and immunotherapeutics to treat rare cancers including blood cancers, two new immune checkpoint inhibitors, and a first of a kind gene therapy to treat bladder cancer.
- While these exciting new advances have the potential to transform patient care, much work is needed to ensure equitable access to these treatments for all populations.

Progress across the continuum of cancer research and patient care improves survival and quality of life for people around the world. In the United States, the annual decline in overall cancer death rate among men, women, children, and adolescents and young adults has accelerated over the past two decades (see **Cancer in 2023**, p. 12) (325). This progress is driven by the dedicated efforts of individuals working throughout the cycle of medical research (see **Figure 4**, p. 27 and **Sidebar 25**, p. 69).

Clinical Research

The rapid pace of progress against cancer is attributable in part to the new and effective treatments that are available today, thanks to the discoveries made through decades of research in basic and translational sciences. These discoveries have deepened our understanding of the cellular and molecular underpinnings of cancer initiation and progression and led to the identification of a range of molecular targets that drive cancer (see **Understanding the Path to Cancer Development**, p. 24). After a potential therapeutic target is identified, it takes many more years of preclinical research before a candidate therapeutic is developed and ready for testing in clinical trials (see **Sidebar 26**, p. 70).

Clinical trials evaluate the safety and efficacy of candidate agents before a preventive intervention or therapeutic can be approved by FDA and used as part of patient care. All clinical trials are critically reviewed and approved by institutional review boards before they can begin and are monitored throughout their duration. There are several types of cancer clinical trials, including prevention trials, screening trials, treatment trials, and supportive or palliative care trials, each designed to answer different research questions (see **Sidebar 27**, p. 71). Clinical studies in which participants are randomly assigned to receive experimental treatment or standard of care treatment are called randomized clinical trials and are considered the most rigorous.

Clinical trials that test candidate therapeutics for patients with cancer have traditionally been done in three successive phases (see **Figure 13**, p. 72). Observations made during the real-world use of a drug after it is approved by FDA can also be utilized to further enhance the use of that drug. The multiphase clinical testing process requires many patients, takes years to complete, and has a high rate of failure, making it extremely costly and one of the main barriers to rapid translation of scientific knowledge into clinical advances (326,327). Identifying and implementing more efficient clinical development strategies are an area of extensive investigation for all stakeholders in medical research (see **Sidebar 1**, p. 13).

SIDEBAR 25

What Is Medical Research?

Medical research, sometimes referred to as biomedical research, as defined by the Organization for Economic Cooperation and Development (OECD), comprises:

The study of specific diseases and conditions (mental or physical), including detection, cause, prevention, treatment, and rehabilitation of persons.

The design of methods, drugs, and devices used to diagnose, support, and maintain the individual during and after treatment for specific diseases or conditions.

The scientific investigation required to understand the underlying life processes that affect disease and human well-being, including areas such as the cellular and molecular bases of diseases, genetics, and immunology.

Any individual whose work falls within the definition of medical research is part of the medical research community. Thus, the medical research community includes, but is not limited to, basic and translational researchers working in a wide range of disciplines, including biology, chemistry, immunology, physics, engineering, and computer science; physician-scientists; health care providers; and population scientists.

Adapted from (163).

Advances in the understanding of cancer biology have enabled researchers from academia and the pharmaceutical industry to develop new approaches to designing and conducting clinical trials. Among the new concepts and designs for clinical trials that have emerged in recent years are the adaptive, main protocol, and platform trials designs (329). These designs allow researchers to modify aspects of the trial design, if needed, by leveraging the accumulating data, thereby increasing the efficiency of the clinical research process. Main protocol, also known as master protocol design, and platform design streamline clinical development and allow the evaluation of multiple new agents by matching the right therapeutics with the right patients earlier, reducing the number of patients who need to be enrolled in the trial, and decreasing the length of time it takes for a new anticancer therapeutic to be tested and made available to patients.

Master protocol can answer multiple clinical questions within a single trial (329). The emergence of this clinical trial design has largely been driven by accumulating knowledge of the genetic mutations that underpin cancer initiation and growth. As one example, I-SPY 2 is one of the longest-running clinical trials that uses a master protocol which provides the regulatory framework to study multiple treatments for breast cancer within a single study (330). The platform design of the I-SPY 2 trial allows new treatments to enter and leave the study with a greater efficiency than traditional clinical trials. The study has led to the FDA approval of several breast cancer treatments, including the molecularly targeted therapeutic neratinib (Nerlynx) (331).

Basket trials are another example of genetic mutation–based master protocol design in clinical trials (see **Figure 14**, p. 73). These trials allow researchers to test one anticancer therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original cancer. As one example, the combination of molecularly targeted therapeutics dabrafenib and trametinib was shown to work against an array of cancer types characterized by a specific genetic feature, or biomarker, called the BRAF V600E mutation, in two recent basket trials including the NCI MATCH study (see **Sidebar 9**, p. 37) (109). Based on the data from these trials, the combination treatment received FDA approval in June 2022 and is now benefiting many patients with cancer (1). Based on a recent analysis, the use of novel trial designs in clinical cancer research has more than tripled, worldwide, over the past decade (332).

As our understanding of cancer biology continues to evolve and we uncover some of the most elusive questions in cancer medicine (see **Cancer Development: Integrating Knowledge**, p. 35) clinical trial designs will need to evolve as well. Additionally, the design and conduct of clinical cancer research need to keep pace with the new wave of technological advances. Novel designs that integrate emerging approaches such as comprehensive tumor profiling (e.g., of genome, transcriptome, proteome, microbiome, and metabolome, among others), artificial intelligence and machine learning, real-world evidence and data, and leverage inputs from patient advocacy communities and social media platforms will be pivotal to advancing the frontier of cancer clinical trials (333).

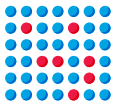
Two of the most pressing challenges that need to be overcome urgently are low participation in cancer clinical trials and a lack of sociodemographic diversity among those who do participate (see **Sidebar 28**, p. 74). Low participation in clinical trials means that many trials fail to enroll enough participants to draw meaningful conclusions about the effectiveness of the anticancer therapeutic being tested. Lack of diversity in clinical studies means that the trial participant population does not

SIDEBAR 26

Therapeutic Development

TARGET VALIDATION

Potential targets identified by discovery science are confirmed to play a causal role in disease development.

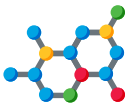


DRUG SCREENING

Large numbers of chemical or biological agents are screened to identify and validate molecules that hit the target.

LEAD IDENTIFICATION

Agents that hit the target are evaluated to determine which ones bind the target with the greatest specificity and have the most promising medicinal properties.



LEAD OPTIMIZATION

The characteristics of lead compounds are optimized to enhance potency and drug-like properties, and to reduce side effects by enhancing specificity.

PRECLINICAL TESTING

Optimized lead compound(s) are tested in cell-based and animal models for effectiveness, potential toxicity, optimal starting dose, and dosing schedule for clinical or "first-in-human" testing. The final compound(s) are considered to be clinical candidate(s).

INVESTIGATIONAL NEW DRUG

One or more clinical candidates are generated through good manufacturing practices and assessed in rigorous good laboratory practice studies before submission to the U.S. Food and Drug Administration for approval for use in clinical trials.

Adapted from (4).

match the actual demographics of the cancer burden under study (334). Underrepresentation in clinical trials compromises the applicability of such research findings to the entire U.S. patient population.

Understanding and eliminating barriers to clinical trial participation for all segments of the population is vital if we are to accelerate the pace of progress against cancer for everyone. Numerous studies have investigated the existing barriers that limit participation of racial and ethnic minorities and other medically underserved populations in cancer clinical trials. These studies have identified a range of factors such as lack of awareness of clinical trials, financial challenges, limited health literacy, inadequate or complete lack of insurance, medical distrust, implicit biases among health care providers, lack of trial availability, and narrow eligibility criteria, among others (13). These barriers operate at individual, systemic, and societal levels (340).

Increased knowledge of the barriers to clinical trial accrual is helping researchers, regulators, and policymakers design and implement evidence-based adaptations that can broaden participant access and promote accrual to clinical research. Such interventions focus on addressing social determinants of health (see **Figure 2**, p. 19), and include decentralizing many of the trial activities to ease patient participation, expanding eligibility criteria, improving the efficiency of data collection, including patient reported outcomes (PRO), and enhancing community outreach and patient navigation efforts to raise awareness of trials. One critical area of focus for all stakeholders in medical research is fostering greater diversity, equity, and inclusion within the clinical research workforce so the workforce will resemble the patient populations it serves.

U.S. lawmakers and FDA are working on legislation and guidelines intended to increase the diversity of clinical trial participants (see **Diversifying and Decentralizing Trials**, p.

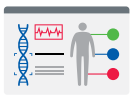
SIDEBAR 27

Types of Clinical Trials

Clinical trials can be designed to address different research questions. Furthermore, many clinical trials can provide answers to multiple questions. As one example, treatment trials—designed to primarily determine clinical outcomes, such as efficacy of an anticancer drug—can also evaluate the impact of the treatment on quality of life. Cancer clinical trials include:

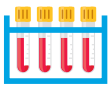
PREVENTION TRIALS

Designed to find out whether people without a cancer diagnosis can reduce their risk of cancer by proactively taking certain actions, such as increasing physical activity and eating healthily.



SCREENING TRIALS

Designed to evaluate new tests to detect cancer before symptoms arise, with the goal of determining whether the screening test will reduce deaths from cancer.



DIAGNOSTIC TRIALS

Designed to test new ways to diagnose a certain type of cancer.

TREATMENT TRIALS

Designed to determine whether new treatments or new ways of using existing treatments—alone or in combinations—are safe for patients and effective in treating cancer.

QUALITY OF LIFE TRIALS

Designed to examine whether patients with cancer can improve their quality of life by taking certain actions, such as attending support groups or exercising more. These trials are also known as supportive care or palliative care trials, and many evaluate the effects of certain cancer medications and treatments on quality of life.

NATURAL HISTORY OR OBSERVATIONAL STUDIES

Designed to learn more about how cancer develops and progresses by following patients with cancer or individuals who are at high risk for developing cancer over a period of years.

CORRELATIVE STUDIES

Designed to examine the efficacy of a candidate anticancer drug by using biomarkers, such as proteins, as indicators of the desired clinical outcome when the effects of the drug on key clinical outcomes, such as reduction in tumor size, may not be apparent.

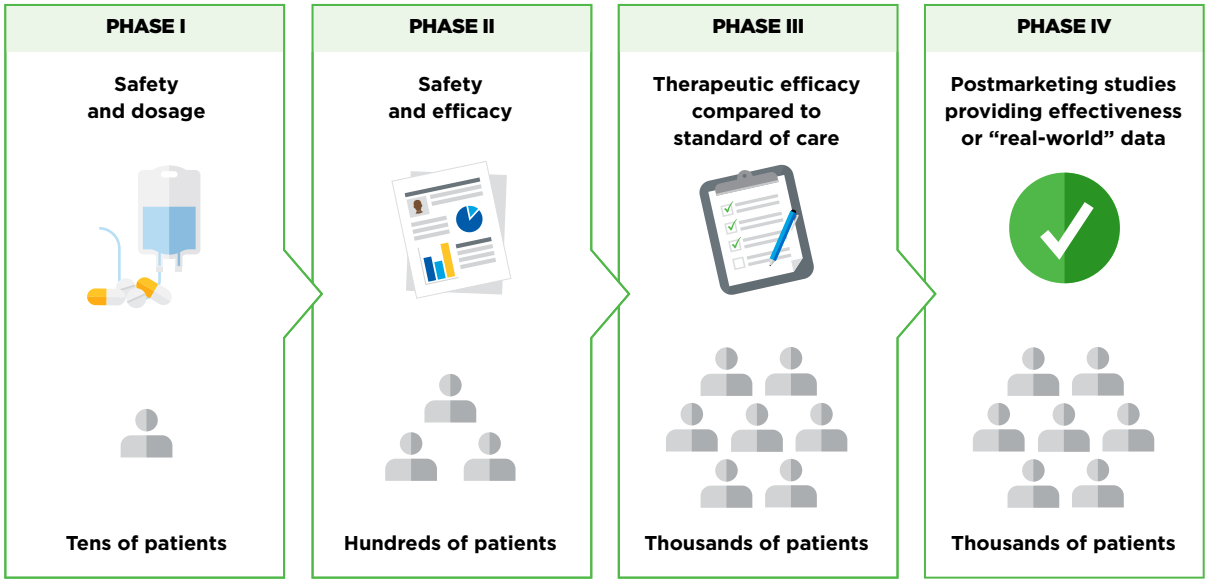
156). These include a diversity action plan which would require researchers and funders of clinical trials to submit concrete goals and needed steps for enrolling specific demographic groups in pivotal studies of new drugs (341). COVID-19, despite its adverse effects on all aspects of cancer research and patient care, enabled researchers to decentralize clinical trial designs, so that lifesaving therapeutics could be brought quickly to as many patients as possible (9). Adaptations implemented by NCI and FDA during the pandemic, including consenting patients remotely, permitting telehealth for routine clinical assessments (see **Sidebar 29**, p. 75), delivering experimental drugs to patients, and allowing the use of local laboratory or imaging facilities accessible to patients have offered a blueprint of success to further revise and reform clinical trials and the drug approval process for the benefit of all patients with cancer.

Progress Across the Clinical Cancer Care Continuum

Research discoveries made as a result of innovative cancer science are continually being translated into new medical products for cancer prevention, detection, diagnosis, treatment, and survivorship. The approval of new medical products, including new anticancer treatments, is not the end of a linear research

FIGURE 13

Phases of Clinical Trials



Clinical trials evaluating potential new therapeutics for treating patients with cancer have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how humans process it, and potential toxicities. Phase I trials are not designed to evaluate efficacy of a therapeutic. Thanks to progress in trial design and conduct, patient response rates in phase I studies have nearly doubled over the past two decades (328). Phase II studies are designed to determine the initial efficacy of an investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care; when successful, the results of these trials can be used by the U.S. Food and Drug Administration (FDA) to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the therapy. In some cases, researchers combine different phases into one clinical trial (labeling depends on the phases combined, e.g., phase I/II or phase III/IV clinical trials), which allows research questions to be answered more quickly or with fewer patients. Sometimes Phase 0 clinical studies are performed prior to traditional clinical trials where low doses of potential therapeutics are administered to small number of patients to determine whether such treatments may have the desired effect.

Adapted from (163).

process. Rather, it is an integral part of the medical research cycle (see **Figure 4**, p. 27) because observations made during the routine use of new medical products can be used to accelerate the pace at which similar products are developed and to stimulate the development of new, more effective products.

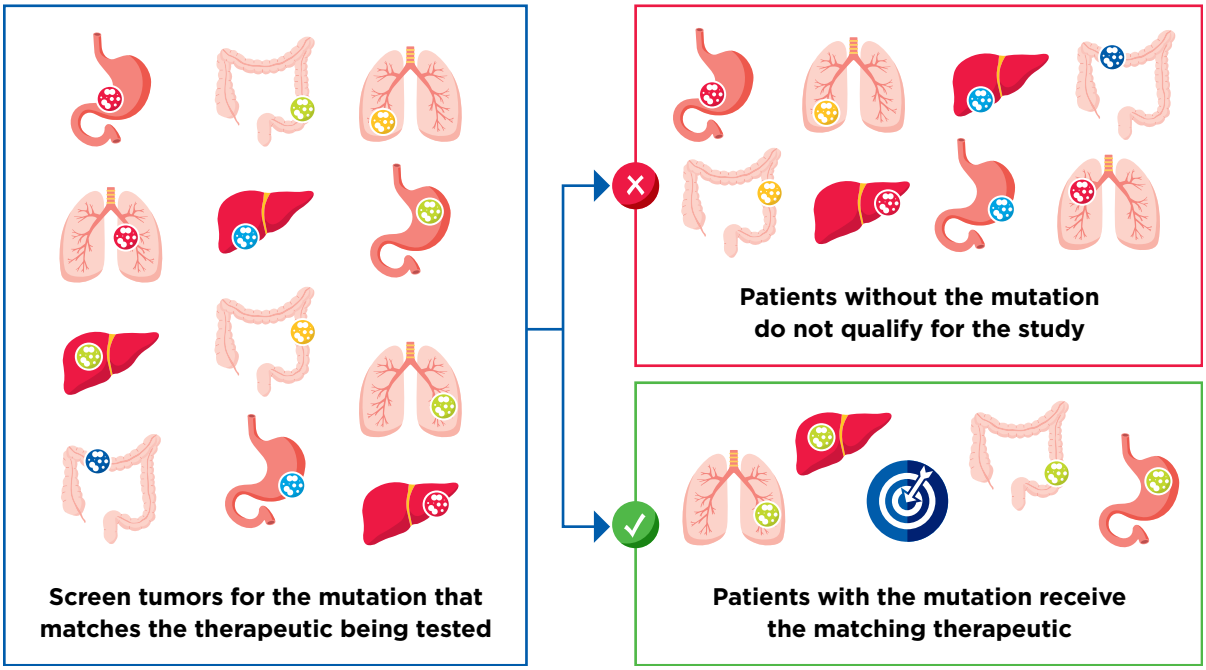
New FDA-approved medical products are traditionally utilized alongside treatments already in use, including surgery, radiotherapy, and cytotoxic chemotherapy, which continue to be the mainstays of clinical cancer care (see **Figure 15**, p. 76). Researchers are also evaluating new ways to refine the use of surgery, radiotherapy, and existing cytotoxic chemotherapeutics to improve survival and quality of life for patients. As one example, a recent clinical trial showed that for patients with early-stage prostate cancer, active monitoring of their disease is a safe alternative to receiving immediate surgery or radiotherapy (346). In most cases, prostate cancer grows slowly. Therefore, the study directly compared the long-term outcomes of the three approaches, prostate removal surgery, radiotherapy, or active monitoring and found that there was no difference in prostate cancer mortality at the 15-year follow-up between the three groups. These data provide hope for patients with prostate cancer who opt for active monitoring to avoid treatment-related adverse effects, such as sexual and incontinence problems.

The following sections focus on the recent advances across the five pillars of cancer treatment including the 14 new anticancer therapeutics approved by the FDA in the 12 months spanning this report, August 1, 2022, to July 31, 2023 (see **Table 3**, p. 77, and **Supplemental Table 2**, p. 192). Also highlighted are the 12 previously approved anticancer therapeutics that received FDA approval for treating additional types of cancer in that period.

FIGURE 14

Mastering Clinical Trial Design

BASKET TRIALS



Recent advances in our understanding of cancer biology have led to novel ways of designing and conducting clinical trials. Notably, cancer clinical trials more frequently utilize novel designs compared to trials in other disease areas. For example, a recent study reported that 27 percent of cancer clinical trials worldwide used these mechanisms in 2022 compared to only 6 percent in all other disease areas (332). One of the new approaches is to use the master protocol to answer multiple questions within a single overall clinical trial. Basket trials are one type of master protocol clinical trial. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, colon, and stomach cancers. This approach allows the clinical testing of new anticancer therapeutics to be streamlined because the therapeutic is matched with the right patients at the start of the trial. This precision approach reduces the number of patients who need to be enrolled in the trial and decreases the length of time it takes for a new anticancer therapeutic to be tested and made available to patients if the trial shows it is safe and effective.

Not discussed are FDA approvals that expand the use of an anticancer therapeutic previously approved for a given cancer type to include treatment with that therapeutic at different timepoints during the course of clinical care or treatment of a different subtype of the same cancer. For example, the August 2022 FDA approval expanded the use of fam-trastuzumab-deruxtecan-nxki (Enhertu), for the treatment of patients with metastatic HER2-low breast cancer that is not removable by surgery. This expansion occurred nearly three years after the molecularly targeted therapeutic was first approved for treating metastatic HER2-positive breast cancer and was based on results from a phase III clinical trial. The study showed that patients with metastatic breast cancer who were treated with fam-trastuzumab-deruxtecan-nxki lived nearly twice as long without their cancer progressing and lived six months longer overall than those treated with standard chemotherapy (352). Fam-trastuzumab-deruxtecan-nxki is the first treatment approved for patients with HER2-low breast cancer subtype, a newly defined subset of HER2-negative breast cancer.

New medical products used across the continuum of clinical cancer care transform lives by improving survival and quality of life. However, not all patients receive the standard of care recommended for the type of cancer with which they have been diagnosed and the stage of cancer at the time of diagnosis (see **Sidebar 30**, p. 78). Thus, it is imperative that all stakeholders committed to driving progress against cancer work together to address the challenge of disparities in cancer treatment because these can be associated with adverse differences in survival. Recent studies have shown that disparities in survival for prostate cancer or multiple myeloma between Black patients and White patients can be eliminated when both population groups have equivalent access to care and to standard treatments (13).

SIDEBAR 28

Disparities in Clinical Trial Participation

To ensure that candidate anticancer therapeutics are safe and effective for everyone who will use them if they are approved, it is vital that the participants in the clinical trials represent the diversity of the patient population. Despite this knowledge, several segments of the U.S. population are underrepresented in clinical trials. Examples of these disparities include the following:

Only 15% and 20%	Between 2012 and 2017, the U.S. Food and Drug Administration approved 59 novel anticancer drugs **based on 64 clinical trials**. Based on U.S. disease prevalence, only 15 percent of these trials adequately represented **Black patients** and only 20 percent adequately represented **Hispanic patients** (335).
Less than 2%	An evaluation of clinical trial **participation among older adult patients** with cancer from January 1, 2014, through June 30, 2020, showed less than 2 percent enrollment (336).
Only 2%	**Black patients represented** 2 percent of the patients **in clinical trials** conducted between January 2010 and August 2022 that led to the approval of 92 immunotherapeutics for the treatment of more than 20 cancer types (337).
POORER access	An evaluation of immunotherapy **clinical trials for metastatic melanoma** conducted in the United States between 2015 and 2021 showed that **rural areas** had significantly poorer access to such trials compared to urban areas (338).
0% and 2%	In the **clinical trial that led to the 2022 FDA approval of mirvetuximab soravtansine-gynx** (Elahere) for the treatment of ovarian cancer (see **Delivering a Cytotoxic Drug Precisely to Ovarian Cancer Cells**, p. 86), 96 percent of **participants** were White, none were Black, only two percent were Hispanic and Asian, respectively (339).

Advances in Cancer Treatment with Surgery

For many years, surgery was the only pillar of cancer treatment (see **Figure 15**, p. 76). Today, it remains the foundation of curative treatment for many patients. Surgery is used in several ways during the care of a patient with cancer (see **Sidebar 31**, p. 79).

Sometimes, additional therapy is given before, after, or around the time of surgery based on specifics of a patient's situation (see **Sidebar 32**, p. 80). Researchers have found that this approach not only improves the surgeon's ability to remove the tumor (for example by shrinking the tumor when given before the surgery), but also increases the patient's overall survival and/or quality of life (359).

Improving Quality of Life After a Cancer Surgery

Despite the immense benefits of surgery for the treatment of cancer, complications are common and can negatively affect patient quality of life. Enhanced recovery after surgery (ERAS) programs are emerging as one approach to address this issue. These comprehensive programs focus on optimizing patient care before, during, and after surgery using strategies that ensure the patient is as physically and emotionally fit for surgery as possible; alleviate the stress of surgery; promote recovery; and reduce the time before patients with cancer can begin adjuvant treatment. Providing patients with an individualized plan that includes exercise, nutrition, stress reduction, and smoking cessation to optimize their physical fitness before surgery is one strategy included in some ERAS programs (360,361). The components of ERAS programs can vary depending on the type of surgery being performed and the center at which the surgery is being performed, but overall, these programs have been promising.

SIDEBAR 29

Telemedicine in Cancer Care

According to NCI, telemedicine, also called telehealth, is the delivery of health care from a distance using electronic information and technology, such as computers, cameras, videoconferencing, satellites, wireless communications, and the Internet. Identifying innovative ways to use telehealth in cancer care and addressing telehealth-related disparities among vulnerable populations are a major focus of a new National Institutes of Health initiative (342).

POTENTIAL BENEFITS

Increased access to health care

Allows access to health services that may not be available to patients locally. Based on a recent study, patients with cancer ranked telehealth higher than in-person care with regard to access and health care provider engagement (343).

Improved health care outcomes

Promotes continuity of care regardless of the location of the patient and the provider, potentially improving overall health outcomes.

Facilitated caregiver and family engagement

Allows caregivers and other family members to participate, which can facilitate patient care.

Decreased infectious exposure

Helps patients with cancer avoid exposure to infectious viruses, bacteria, and other pathogens. Many patients are immunocompromised because of their cancer or treatments.

Reduced costs and/or work-related adjustments

Helps patients with cancer save time, travel, and money (344).

POTENTIAL DRAWBACKS

Widened health care disparities

Recent data indicate that patients with cancer from racial and ethnic minority and medically underserved populations are more likely to experience unsuccessful telemedicine visits (345). Lack of access to infrastructure that supports telehealth (e.g., computer, smartphones, Internet) is disproportionately experienced by patients from medically underserved populations and may widen cancer disparities.

Rapidly changing policies and reimbursement rules

The fast-paced nature of telemedicine may make it harder for health care providers to keep up with health care laws, reimbursement policies, and privacy protections.

Costly initial implementation

Implementing telemedicine at a health care facility, including restructuring information technology staff, purchasing necessary equipment, and training clinicians and support staff, takes time and costs money.

Security of personal health data

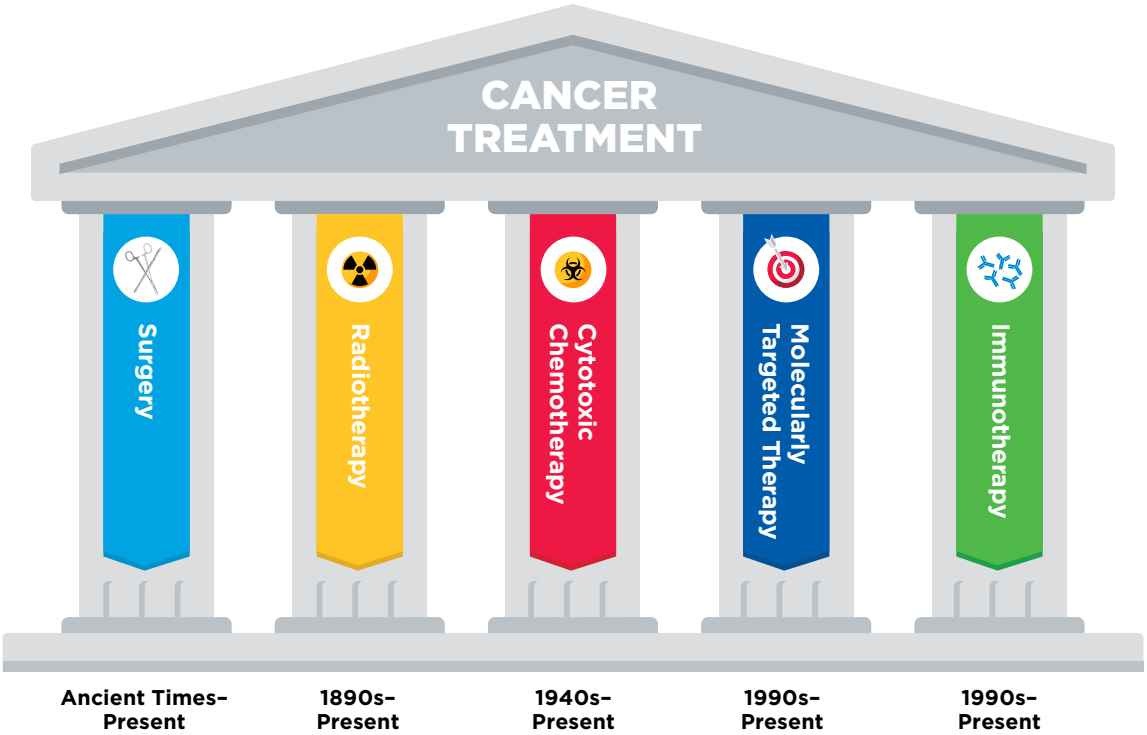
The security of personal health data transmitted electronically is also a concern, which can be mitigated by employing a Health Insurance Portability and Accountability Act (HIPAA)-compliant telemedicine platform.

Adapted from (9).

One study found that among patients undergoing surgery for tumors that have metastasized to the spine, those who participated in an ERAS program had reduced blood loss, shorter hospitalization, and significant reduction in opioid pain reliever utilization compared to those who did not participate (362). Another study showed that among patients undergoing surgery for colorectal cancer, those who participated in an individualized plan that included exercise, nutritional

FIGURE 15

The Pillars of Cancer Treatment



The cancer treatment paradigm is built upon what physicians often refer to as the "pillars" of cancer treatment. For centuries, surgery was the only treatment for cancer (347). In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar (348). The foundations for the third treatment pillar—cytotoxic chemotherapy—were established in the early 1940s, with the use of a derivative of nitrogen mustard to treat lymphoma (349). These three pillars—surgery, radiotherapy, and cytotoxic chemotherapy—continue to be critical components of cancer treatment. Introduction of the first molecularly targeted therapeutics in the late 1990s led to the establishment of a fourth pillar, molecularly targeted therapy (350). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (351). Continued evolution of new approaches, such as analysis of tumors aided by artificial intelligence, enhanced molecular imaging, and validation of new biomarkers, plays a critical role in advances in each of these therapeutic areas.

intervention, and psychological support had fewer medical complications and better recovery postsurgery than those who did not participate in such programs (363).

Other approaches to reducing the complications during and after surgery and improving quality of life postprocedure are to perform less extensive and minimally invasive surgeries, such as robotic surgeries or to identify a subset of patients who could skip surgery altogether.

As one example, data from a recent clinical trial showed that for certain patients with early-stage non–small cell lung cancer (NSCLC), surgical removal of only part of the affected lobe of lung is an effective treatment option (364). The study, which compared the outcomes of patients who had their entire lobes removed to those who had only the tumor-affected regions removed, showed that the 5-year overall survival was similar in the two groups. While the study participants represent only a select subgroup of patients with lung cancer, these data are important considering that removal of less lung tissue can preserve lung function, especially for older adults and those with compromised lung capacity, such as patients with a prior lung cancer.

Studies have shown that less invasive surgeries may benefit patients since they can minimize postprocedural complications without compromising and sometimes improving long-term outcomes (365-367). As one example, in a recent clinical trial, patients with locally advanced stomach cancer who underwent a minimally invasive procedure had significantly lower long-term complications after surgery, but similar 5-year overall and relapse-free survival rates compared to those who had

TABLE 3

Newly FDA-approved Anticancer Agents: August 1, 2022-July 31, 2023

TYPE OF TREATMENT	GENERIC NAME	TRADE NAME	WHAT IS IT?	APPROVED FOR?
Surgery, Chemotherapy, Radiotherapy	flotufolastat fluorine-18	Posluma	Imaging agent	Certain type of prostate cancer
	pafolacianine*	Cytalux	Imaging agent	Certain type of lung cancer
Molecularly Targeted Therapy	adagrasib§	Krazati	Cell-signaling inhibitor	Certain type of lung cancer
	fam-trastuzumab deruxtecan-nxki§	Enhertu	Antibody–drug conjugate	Certain type of lung cancer*
	selpercatinib	Retevmo	Cell-signaling inhibitor	Solid tumors carrying certain type of genetic mutation*
	mirvetuximab soravtansine-gynx§	Elahere	Antibody–drug conjugate	Certain type of ovarian cancer
	elacestrant	Orserdu	Antihormone	Certain type of breast cancer
	futibatinib	Lytgobi	Cell-signaling inhibitor	Certain type of bile duct cancer
	dabrafenib + trametinib	Tafinlar + Mekinist	Cell-signaling inhibitors	Certain type of glioma*
	tucatinib + trastuzumab	Tukysa + Herceptin	Cell-signaling inhibitors	Certain type of colorectal cancer*
	olutasidenib§	Rezlidhia	Epigenome modifying agent	Certain type of leukemia
	quizartinib§	Vanflyta	Cell-signaling inhibitor	Certain type of leukemia
	pemigatinib	Pemazyre	Cell-signaling inhibitor	Certain types of blood cancer*
	pirtobrutinib	Jaypirca	Cell-signaling inhibitor	Certain types of lymphoma
	zanubrutinib	Brukinsa	Cell-signaling inhibitor	Certain types of lymphoma*
	talazoparib	Talzenna	DNA repair inhibitor	Certain type of prostate cancer*
Immunotherapy	tremelimumab + durvalumab	Imjudo + Imfinzi	Immune checkpoint inhibitors	Certain type of liver and lung cancers
	retifanlimab-dlwr	Zynyz	Immune checkpoint inhibitor	Certain type of skin cancer
	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of gallbladder cancer*
	atezolizumab	Tecentriq	Immune checkpoint inhibitor	Alveolar soft part sarcoma*
	nadofaragene firadenovec-vncg	Adstiladrin	Gene therapy	Certain type of bladder cancer
	teclistamab-cqyv	Tecvayli	Bispecific antibody	Multiple myeloma
	mosunetuzumab-axgb	Lunsumio	Bispecific antibody	Certain type of lymphoma
	epcoritamab-bysp	Epkinly	Bispecific antibody	Certain type of lymphoma
	glofitamab-gxbm	Columvi	Bispecific antibody	Certain type of lymphoma

*New cancer type approved 2022-2023
§Requires a companion diagnostic

open surgeries (366). Additionally, two retrospective analyses showed improved disease-free and overall survival for patients with pancreatic cancer and reduced morbidity during surgery for patients with liver cancer who underwent minimally invasive surgeries compared to those who received open surgeries (365,367). Yet another report from an early-stage clinical trial showed that a selected subset of patients with breast cancer who responded remarkably well to neoadjuvant chemotherapy could potentially forgo surgery without risking tumor recurrence (368).

Recent studies have also identified subsets of patients who could skip surgery altogether without compromising outcomes. In a clinical trial, women who had early-stage breast cancer with defined clinical characteristics had equally good overall survival whether they received radiotherapy delivered to the lymph nodes in their underarms (axillary radiotherapy), or an invasive surgical procedure to remove these lymph nodes (axillary lymph node dissection) (369). Notably, axillary lymph node dissection is associated with a significantly higher rate of morbidity, particularly lymphedema, which causes swelling

SIDEBAR 30

Disparities in Cancer Treatment

Research is constantly powering the development of new cancer treatments. However, medically underserved populations experience numerous barriers to quality cancer care and are less likely to receive recommended treatments. Examples of these disparities include:

29% less likely	Patients with non-small cell lung cancer living in **neighborhoods with the lowest education** or **income levels** were 29 percent **less likely to receive immunotherapy** compared to those living in the most educated or high-income areas (353)
Significantly LONGER	**Time between cancer diagnosis and the initiation of first treatment** is significantly longer for **Black patients** (median = 16.5 days) compared to White patients (median = 9.5 days) (354).
The LONGEST	Median **travel times** to access cancer care are the **longest for American Indian** or **Alaska Native children** and **adolescents** and **young adults** (AYAs) compared to the overall population of children and AYA patients (355).
38% more likely	**Hispanic men** with metastatic prostate cancer are 38 percent more likely **to experience treatment delays** compared to non-Hispanic White men (356).
21% more likely	**Patients from rural areas** are 21 percent more likely to **fail to undergo surgery** for potentially removable non-small cell lung cancer compared to those from urban areas (357).
26% less likely	**Patients with breast cancer** living in historically **redlined areas** are 26 percent less likely to receive surgery and they have **poorer survival** (358).

in the arms that can cause pain and problems in functioning. These risks are drastically reduced if radiotherapy is given instead and suggests radiation rather than surgery should be the preferred approach in these patients.

While less invasive approaches to surgery such as those described above are promising, before they can become standard of care, it is vital that they are shown in rigorous, well-designed, larger clinical trials to have no adverse effect on long-term patient survival.

Visualizing Lung Cancers More Precisely During Surgery

Lung cancer is the leading cause of cancer deaths in the United States with an estimated 127,070 deaths predicted in 2023 (28). While surgery is the standard treatment and provides the best chance to cure early-stage lung cancer, up to 55 percent of people with lung cancer who undergo surgery with curative intent have a recurrence (370). Therefore, it is vital that the entire tumor is removed during surgery. Surgeons rely on either imaging tumors before surgery, visually inspecting tumors under normal white light during surgery, or examining tumors by touch to identify cancerous tissue. Unfortunately, some lung lesions can be difficult to visualize, particularly if they are small, beneath the surface of the lung, or a type of lesion characterized by increased opacity of the lung called ground glass opacity, which is being increasingly diagnosed as the rates of lung cancer screenings rise (371,372).

In December 2022, the FDA approved pafolacianine (Cytalux), a folate receptor–targeted fluorescent agent, as the first and only targeted molecular imaging agent that illuminates lung cancers and enhances surgeons' ability to see cancer in real time as they operate. Molecular imaging using pafolacianine during surgery enables the detection of lung lesions that may have otherwise been missed. Pafolacianine was previously approved to assist surgeons in visualizing hard to detect lesions in adult patients with ovarian cancer during surgery (1). Pafolacianine

SIDEBAR 31

Using Surgery for Cancer Treatment

Surgery can be used in several ways during the care of a patient with cancer:

To diagnose cancer

Surgery is performed to obtain a tumor sample for diagnosing cancer.

To stage cancer

Surgery is performed to determine how far the cancer has spread from the site of origin so that the best treatment plan can be developed for the patient.

To cure cancer

Surgery is performed to remove the entire tumor if cancer is confined to one area of the body.

To debulk cancer

Surgery is performed to remove only part of the tumor if it is very large and/or located very close to important organs or tissues.

To ease problems caused by cancer

Surgery is performed to remove tumors that are causing pain, pressure, or blockages in patients with advanced-stage cancer.

SURGERY FOR PATIENTS WITH CANCER CAN BE OPEN OR MINIMALLY INVASIVE.

Open surgery

When a surgeon makes one or more large cuts to remove the tumor, some surrounding healthy tissue, and maybe some nearby lymph nodes.

Minimally invasive surgery

When a surgeon makes one or more small cuts, inserting a long, thin tube with a tiny camera, called a laparoscope, into one of the small cuts. The camera projects images from the inside of the body onto a monitor, which allows the surgeon to see what is happening. Special surgery tools are inserted through other small cuts to remove the tumor and some healthy tissue.

Sometimes **robotic platforms** are used to perform minimally invasive surgeries; this approach provides a magnified stereoscopic vision of the tumor and internal organs and a better ability for surgeons to work within confined spaces.

binds to folate receptors, a protein that is commonly found on the surface of many cancers and illuminates tumor cells under near-infrared light. The agent is administered via intravenous infusion within 24 hours before surgery and assists surgeons in visually identifying additional malignant tissue to be removed during the procedure.

The approval in lung cancer was based on a clinical trial that evaluated the utility of pafolacianine in visualizing tumors in the lungs that may otherwise be undetected with conventional visualization under white light (373). Molecular imaging using pafolacianine during surgery identified in 19 percent of patients primary lung nodules that surgeons could not find using white light and palpation; additionally, pafolacianine revealed in eight percent of patients additional lesions that were completely missed using white light. The expanded approval of pafolacianine represents a significant advancement in the treatment of lung cancer by enhancing detection of lung tumors during surgery, improving the ability to remove them completely, and reducing the probability of leaving behind cancerous tissue.

Improvements in Radiation-based Approaches to Cancer Care

Radiotherapy is the use of high-energy rays (e.g., gamma rays and X-rays) or particles (e.g., electrons, protons, and carbon nuclei) to control or eradicate cancer. Discovery of X-rays in 1895 allowed visualization of internal organs at low doses, and the effective use of X-rays at high doses to treat a breast cancer patient a year later established radiotherapy as the second pillar of cancer treatment (see **Figure 15**, p. 76). Radiotherapy plays a central role in the management of cancer and works primarily by damaging DNA, leading to cancer cell death. The use of radiotherapy in treatment and management of cancer continues to increase, as indicated by a 16.4 percent increase in radiation facilities across the United States between 2005 and 2020 (374).

There are many types and uses of radiotherapy (see **Sidebar 33**, p. 81). However, it is important to note that radiotherapy may also have harmful side effects, partly because of the radiation-induced damage to healthy cells surrounding the tumor tissue (375).

SIDEBAR 32

Commonly Used Terms and Benchmarks in Clinical Studies

Search...

ADJUVANT THERAPY

An anticancer therapy that is administered after surgery to eradicate as many residual cancer cells as possible.

COMPLETE RESPONSE

Absence of cancer detectable by any available methods, such as imaging.

DURATION OF RESPONSE

Time from documentation of disease response to disease progression.

MEDIAN SURVIVAL

The length of time from either the date of cancer diagnosis or the start of treatment that half of the patients in a group of patients diagnosed with the disease are still alive.

NEOADJUVANT THERAPY

An anticancer therapy that is administered before surgery to reduce the tumor size.

OBJECTIVE RESPONSE RATE

Percentage of patients whose disease decreases (partial response) and/or disappears (complete response) after treatment.

OVERALL RESPONSE RATE

Proportion of patients with reduction in disease burden of a predefined amount.

OVERALL SURVIVAL

Time from start of the clinical study until death from any cause.

PLACEBO

A substance that has no therapeutic effect and is used as a control (i.e., comparison group) when testing new drugs.

PROGRESSION-FREE SURVIVAL

Time from start of the clinical study until disease progression or death.

RECURRENT OR RELAPSED CANCER

Cancer that has come back or recurred, usually after a period of time during which the cancer could not be detected.

REFRACTORY DISEASE

Cancer that does not respond to treatment. Also called resistant cancer.

RESPONSE RATE

Measurement of disease size, usually using a scan or X-ray. Typically reflected as the percentage of patients whose cancer shrinks or disappears after treatment.

STANDARD OF CARE

Treatment that is accepted by medical experts as a proper treatment for a certain type of cancer and that is widely used by health care professionals. Also called best practice, standard medical care, and standard therapy. In some randomized trials testing a new treatment, the comparison group is the standard of care treatment.

SYSTEMIC THERAPY

Any type of cancer treatment that targets the entire body, for example, chemotherapy.

Researchers are continuously working on making radiotherapy safer and more effective and identifying when radiotherapy can be avoided without affecting the chances of survival for patients. As one example, a recent clinical trial showed that older adult patients with small, early-stage breast cancer may forgo radiation after breast conserving surgery without compromising their overall survival (376). Traditionally, in these patients, surgery has been followed with radiotherapy to reduce the risk of cancer recurrence. However, radiotherapy can lead to a range of potential side effects including pain, minor risks of organ damage and secondary cancer, as well as time and financial losses. Adverse effects are especially challenging for older adults, many of whom have other comorbidities. The new evidence provides these patients with the option for a less aggressive course of action.

Another clinical trial showed that radiation therapy before initial surgery may not be needed for patients with locally advanced rectal cancer that has spread locally within the rectum but not to other organs (377). Traditionally, these patients receive radiation combined with chemotherapy, also known as chemoradiotherapy, before surgical removal of their tumors. Chemoradiotherapy shrinks the tumor making it easier to remove and helping to prevent recurrence. Data from the recent clinical trial showed that chemotherapy alone before

SIDEBAR 33

Using Radiation in Cancer Treatment

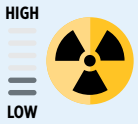
There are two major applications of ionizing radiation in cancer care:

TREATMENT OF CANCER

Radiotherapy, or radiation therapy, uses high-energy radiation to control and eliminate the disease.

DETECTION OF CANCER

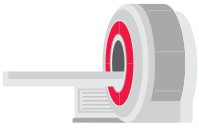
Radiology largely uses low-energy radiation to image tissues to diagnose the disease.



TYPES OF RADIOTHERAPY

External beam radiotherapy

Delivers radiation, usually photons (X-rays) or electrons, to the tumor from outside the body; it is the most common form of radiotherapy.



There are several types of external beam radiotherapy:

- **Conventional external beam radiation therapy** delivers a high-energy X-ray beam from one or more directions and is primarily used when high precision is not required.
- **Three-dimensional conformal radiotherapy (3DCRT)** delivers high-energy X-rays via multiple beams that, with the help of computed tomography and/or magnetic resonance imaging, enable more precise planning to best target the shape and size of the tumor.
- **Intensity-modulated radiotherapy**—a refinement of 3DCRT—delivers radiation by dividing each beam into many "beamlets," each of which can have a different intensity, to achieve improved conformality.
- **Intraoperative radiation therapy** delivers electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures, or to the tumor cavity immediately after cancer removal.
- **Stereotactic radiotherapy** delivers radiation to very well-defined smaller tumors, typically using more than eight beams with the help of a highly sophisticated immobilization and imaging system. It is used in both stereotactic radiosurgery (to treat tumors of the brain and central nervous system) and stereotactic body radiotherapy (to treat small tumors within the rest of the body).

Particle therapy

Delivers radiation doses by protons or carbon ions, instead of X-rays, to the tumor with a dose distribution that better spares the exposure of surrounding tissue, because these particles deposit most of their energy in the target. Although of great interest, proton facilities are much more expensive than traditional facilities, and the overall benefit to patients remains to be defined.

Brachytherapy

Delivers radiation by placing small radioactive sources in or next to the tumor either temporarily or permanently.

Radioisotope therapy

Delivers radiation to the tumors via systemic ingestion or infusion of radioisotopes.

USES OF RADIOTHERAPY

Curative radiotherapy

Used to eliminate cancers, often in combination with systemic therapy.

Neoadjuvant radiotherapy

Used to shrink a tumor so that it can be subsequently treated by a different method such as surgery.

Adjuvant radiotherapy

Used to eliminate any remaining cancer, often directed to the tumor cavity following prior surgical removal.

Palliative radiotherapy

Used to reduce or control symptoms of disease when cancer is considered incurable.

Salvage radiotherapy

Used to treat cancer after the cancer has not responded to other treatments but could be successfully controlled by radiotherapy.

surgery was just as effective as chemoradiotherapy at keeping the cancer at bay (377).

Researchers are also designing novel radiotherapeutics, to be used alone or in combination with other treatments, to target more cancer types and benefit more patients. Additionally, technological innovations, such as the development of advanced imaging and sophisticated computer analytic programs assisted by AI, are helping optimize the delivery of the radiation to the tumor while minimizing exposure to normal tissues (378). As one example, Magnetic Resonance Imaging (MRI)-guided radiotherapy (MRgRT) is a novel technology with the potential to transform radiotherapy for many patients including those with prostate cancer (379). MRgRT provides the ability to image tumors and internal organs with MRI and adapt the radiotherapy plan in real-time while the patient is undergoing the procedure. Unlike traditional radiotherapy, MRgRT allows monitoring of changes in tumor size and positional changes of internal organs during each treatment to achieve a more accurate delivery of the radiation dose. This is particularly critical for rapidly changing tumors and body regions, such as the prostate, where there could be dramatic changes in organ position during each treatment.

Imaging Prostate Cancer More Clearly

Prostate cancer is the most common type of cancer in men in the United States. In 2023, an estimated 288,300 new cases will be diagnosed and 34,700 men will die from the disease.

Prostate cancer that is confined to the prostate is usually treated with surgery or radiation therapy. Unfortunately, many patients with primary prostate cancer have detectable metastases in their pelvic lymph nodes, which are correlated with a risk for cancer recurrence. Surgical procedures known as pelvic lymph node dissection or pelvic lymphadenectomy are used to detect pelvic node lesions, but their use is imprecise and limited to a planned surgical area. An ideal detection method for metastatic prostate cancer would locate tumors in pelvic nodes as well as more distant sites. The more precise a patient's diagnosis, the easier it is for a health care provider to tailor the treatment to ensure that it is as effective and safe as possible. Notably, despite surgery or radiotherapy many patients with prostate cancer have local or distal recurrences within 10 years.

Among the tools physicians use to make cancer diagnoses is positron emission tomography–computed tomography (PET–CT or PET), a form of imaging that can help physicians precisely locate the position of a patient's cancer within the body and determine the extent to which the cancer may have spread. Before a PET scan, patients are injected with a radioactive imaging agent. The PET scan detects cancer by identifying where in the body the radioactive agent accumulates.

In May 2023, FDA approved flotufolastat fluorine-18 (Posluma) for PET imaging of PSMA-positive lesions in patients with prostate cancer with suspected metastasis or with suspected recurrence based on elevated serum PSA level. PSA is a secreted biochemical marker that is used to screen individuals for prostate cancer and for predicted recurrence of the disease among patients who have received treatment. PSMA is a protein that is present in abundance on the surface of more than 90 percent of primary and metastatic prostate cancer cells. Flotufolastat F-18 contains a short peptide sequence that binds to PSMA and is internalized by cells that express PSMA. Flotufolastat F-18 also contains the radioisotope fluorine-18 which enables PET imaging of the prostate and other areas of the body where prostate cancer may have spread. Clinicians can use this information to decide which patient should receive treatment and spare others from unnecessary procedures.

Findings from two clinical trials that FDA used to approve flotufolastat F-18 indicate that detection of prostate cancers using this approach may help physicians make the best treatment decisions for patients (380). One study demonstrated a higher specificity of flotufolastat F-18 for the detection of pelvic lymph node metastasis, compared to standard histopathology, in patients with PSMA-positive lesions. Flotufolastat F-18 provided valuable information that would likely result in changes in clinical management for these patients. In the second study, flotufolastat F-18 demonstrated high prostate cancer recurrence detection rates in patients who had suspected disease recurrence based on elevated PSA levels.

Advances in Treatment with Cytotoxic Chemotherapy

Cytotoxic chemotherapy—use of chemicals to kill cancer cells—was first introduced as a pillar of cancer treatment in the early to mid-20th century (349). Chemotherapy remains a backbone of cancer treatment and its use is continually evolving to minimize potential harms to patients with cancer, while maximizing its benefits.

As with surgery, chemotherapy is more commonly used to treat cancer in combination with one or more additional types of treatments. Furthermore, FDA continues to grant approvals to newer and more effective chemotherapeutics. FDA also routinely expands the use of previously approved chemotherapeutics for additional cancer types through review of new clinical trials as well as by monitoring of current real-world use of such agents. The FDA Project Renewal leverages expertise of clinical researchers to review existing published literature on drug utilization and maintain updated labeling of older, commonly prescribed anticancer therapeutics. As one example of this approach, in December 2022, FDA approved updated labeling for the chemotherapeutic capecitabine (Xeloda) which included new indications and dosing regimens for capecitabine tablets.

Treatment with cytotoxic chemotherapeutics can have adverse effects on patients. These effects can occur during treatment

and continue in the long term, or they can appear months or even years later. Health care providers and researchers are investigating different approaches to make chemotherapeutics safer for patients. Areas of ongoing investigation include designing modifiable chemotherapeutics, e.g., with "on" and "off" switches, that are selectively delivered to tumors while sparing healthy tissue; evaluating less aggressive chemotherapy regimens which can allow patients the chance of an improved quality of life without compromising survival; and identifying biomarkers such as circulating tumor DNA to correctly predict which patients will or will not benefit from chemotherapy, among other approaches (381-383).

Notably, due to complex reasons, the United States is amid a significant chemotherapeutic shortage. The situation is affecting many patients and disrupting clinical research nationwide. It is imperative that all stakeholders in health care come together and identify ways to address these shortages at the earliest possible time (see **Addressing Cancer Drug Shortages**, p. 158).

Advances in Treatment with Molecularly Targeted Therapy

Remarkable advances in our understanding of the biology of cancer, including the identification of numerous genetic mutations that fuel tumor growth, set the stage for a new era of precision medicine, an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the individual patient and the characteristics of his or her cancer dictates the best treatment option for the patient (see **Understanding the Path to Cancer Development**, p. 24).

Therapeutics directed to molecules influencing cancer cell multiplication and survival target tumor cells more precisely than cytotoxic chemotherapeutics, which generally target all rapidly dividing cells, and thereby limit damage to healthy tissues. The greater precision of these molecularly targeted therapeutics tends to make them more effective and less toxic than cytotoxic chemotherapeutics. As a result, they are not only saving the lives of patients with cancer, but also allowing these individuals to have a higher quality of life. Unfortunately, because of multilevel barriers to health care, there are disparities in the utilization of molecularly targeted treatments among patients from racial and ethnic minorities and other medically underserved populations (13). It is vital that ongoing research and future public health policies are aimed to ensure equitable access to precision cancer medicine including tumor genetic testing and the receipt of molecularly targeted therapeutics for all patients.

In the 12 months spanning August 1, 2022, to July 31, 2023, FDA approved seven new molecularly targeted anticancer therapeutics (see **Table 3**, p. 77). During this period, FDA also approved nine previously approved molecularly targeted anticancer therapeutics for treating additional types of cancer.

Expanding Treatment Options for Patients with Lung Cancer

Lung cancer is the second most diagnosed cancer in both men and women and the most common cause of cancer death. More than 127,000 deaths are estimated to occur from the disease in 2023 in the United States (28). Decades of basic and translational research have significantly increased our understanding of the genetic changes that drive lung cancer growth and have fueled the development of therapeutics that target these changes (see **Figure 1**, p. 14) (28). Two recent FDA decisions have the potential to drive more progress against lung cancer because they have provided new molecularly targeted therapeutic options for certain patients with the disease.

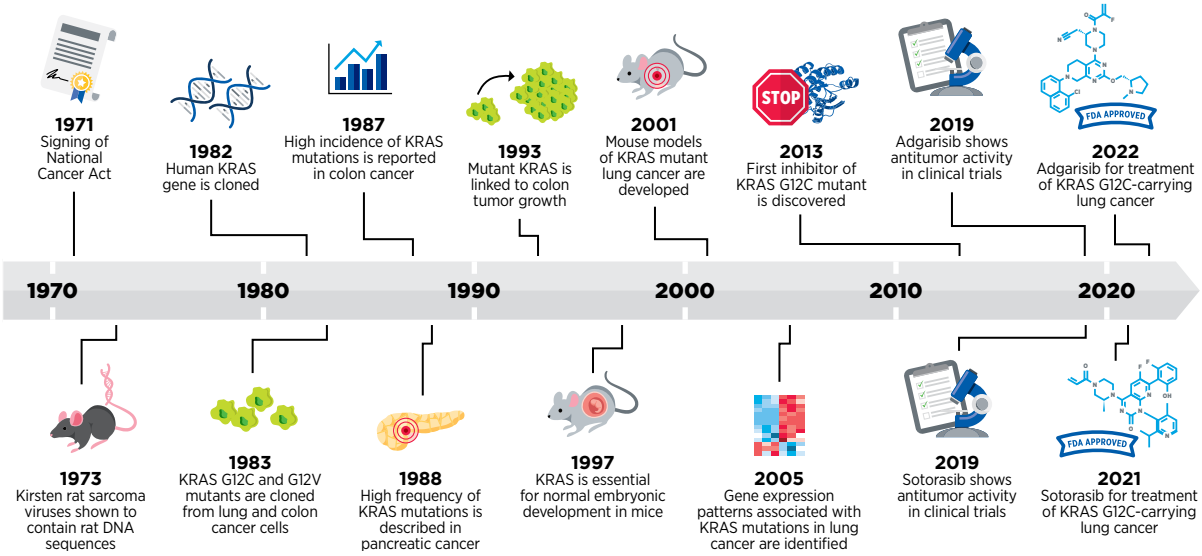
About 81 percent of lung cancers diagnosed in the United States are classified as non–small cell lung cancers (NSCLC) and approximately 25 percent of patients with NSCLC carry mutations in the gene that is responsible for producing KRAS, an essential protein needed for growth and survival of normal lung cells, but which can contribute to cancer if mutated (28,384). Mutated *KRAS* represents one of the most common genetic alterations responsible for the development and progression of human cancers. Patients with NSCLC harboring KRAS mutations often develop resistance to standard treatments such as chemotherapy, radiation therapy, and immunotherapy, and only 25 percent of these patients live five years or more after diagnosis (438). The most common KRAS mutation in patients with NSCLC is known as KRAS G12C, an alteration that is more frequently found in individuals who smoke currently or have smoked previously. The G12C mutation causes KRAS protein to prefer an "on" or "active" state, leading to uncontrollable cell growth that can form tumors.

Historically, KRAS has been considered an undruggable target because of the difficulties in designing a therapeutic that could selectively bind and inhibit KRAS in cancers. Despite major breakthroughs in selective targeting of a range of other genetic drivers of NSCLC, no effective treatment options were available for patients with KRAS G12C until two years ago. Thanks to enhanced understanding of KRAS biology and unprecedented progress in structural biology and drug development, in May 2021, sotorasib (Lumakras) became the first ever molecularly targeted therapeutic approved by the FDA for the treatment of patients with NSCLC with the KRAS G12C mutation (see **Figure 16**, p. 84) (4).

In December 2022, FDA approved a new molecularly targeted therapeutic, adagrasib (Krazati), for adult patients with locally advanced or metastatic NSCLC that has the KRAS G12C mutation, as determined by an FDA-approved test, and who have received at least one prior systemic treatment such as

FIGURE 16

Milestones in the Journey to Target the Undruggable KRAS



Decades of research led to the development and approval of sotorasib in May 2021 and adagrasib in 2022. The relationship between *RAS* genes and lung cancer was first described in 1983, and subsequent discoveries led to the evaluation of several KRAS targeted therapeutics that work directly (by inhibiting KRAS function) or indirectly (by blocking other proteins that carry out KRAS's function in the cell). The first clinical trials investigating the efficacy of indirect KRAS inhibitors were carried out in the early 2000s. Since then, many KRAS inhibitors have been developed and tested but largely failed because of limited efficacy and/or toxicity to normal tissues. Targeting KRAS with small molecular inhibitors has been particularly challenging because the three-dimensional form of the protein lacks an accessible or "druggable" pocket, posing a significant challenge to developing molecularly targeted drugs that are selective for the mutated protein. With the availability of deeper insights into the mutational landscape of lung cancer and breakthroughs in drug design, researchers were able to develop the first KRAS inhibitor, sotorasib (Lumakras), which was approved in May 2021 by FDA based on promising results from preclinical and clinical studies. In December 2022, FDA approved a second KRAS inhibitor, adagrasib (Krazati).

chemotherapy or immunotherapy. The FDA also approved companion diagnostics (see **Sidebar 34**, p. 85), QIAGEN therascreen KRAS RGQ PCR kit (tumor tissue-based) and Agilent Resolution ctDx FIRST Assay (blood-based) to help identify patients with NSCLC carrying the KRAS G12C mutation. Both sotorasib and adagrasib bind to KRAS G12C protein and lock it in an inactive state thus blocking tumor growth.

The FDA approval of adagrasib was granted after it was shown in a phase II clinical trial that 43 percent of the patients who received the targeted therapeutic had complete or partial tumor shrinkage and continued to respond for a median of 8.5 months without their cancer progressing (384). A critical finding from the clinical trial was that adagrasib was able to reach the brains of patients with NSCLC and shrink tumors that had metastasized to the brain (385). While additional research is needed to confirm therapeutic activity in the brain, these data are extremely encouraging considering recent findings that 27 to 42 percent of patients with NSCLC whose tumors harbor the KRAS G12C mutation may have central nervous system (CNS) metastases at diagnosis, and such metastases are associated with a poor prognosis (384).

Another major advance against lung cancer during the 12 months covered in this report is the FDA approval of fam-trastuzumab deruxtecan-nxki (Enhertu) for adult patients with surgically unremovable or metastatic NSCLC whose tumors have a type of mutation in the human epidermal growth factor receptor 2 (*HER2*) gene, called an activating mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy. The FDA also approved Oncomine Dx Target Test (tissue-based) and Guardant360 CDx (blood-based) as companion diagnostics to test patients for activating HER2 mutations.

HER2-mutated NSCLC, which accounts for three percent of all NSCLC cases, is associated with female sex, never-smoking history, and a poor prognosis. Furthermore, this type of NSCLC has a higher incidence of brain metastases than NSCLC without HER2 mutations or with other mutations (386,387).

SIDEBAR 34

Companion Diagnostics

The effective use of anticancer therapeutics targeting defined cancer-driving molecular abnormalities often requires tests called companion diagnostics. Using tumor tissue or blood samples, companion diagnostic tests can identify whether a patient's cancer has a specific genetic alteration or biomarker that is targeted by the drug.

COMPANION DIAGNOSTICS:

Are **stringently tested** for accuracy, sensitivity, and fidelity;

Are **regulated** by the U.S. Food and Drug Administration;

Accurately match patients with a specific therapy;

Allow patients to receive a treatment to which they are most likely to respond; and

Allow patients identified as very **unlikely to respond to forgo treatment** with the therapeutic and thus be spared the cost and adverse side effects.

Adapted from (163).

Fam-trastuzumab deruxtecan-nxki is a type of molecularly targeted therapeutic called an antibody–drug conjugate. It comprises a cytotoxic agent, deruxtecan, attached to the HER2-targeted antibody, trastuzumab (Herceptin), by a linker. When the antibody attaches to HER2 protein on the surface of lung cancer cells, the antibody–drug conjugate is internalized by the cells. This leads to deruxtecan being released from the linker and the antibody. Once free, the deruxtecan is toxic to the cancer cells, which ultimately die.

The approval of fam-trastuzumab deruxtecan-nxki was primarily based on the results of a phase II clinical trial in which treatment with the HER2-targeted therapeutic shrank tumors in nearly 60 percent of the study participants (388). Among patients whose tumors shrank, the treatment kept their lung cancer at bay for nearly 9 months. While fam-trastuzumab deruxtecan-nxki has previously been approved for the treatment of patients with HER2-driven breast and gastric cancers (4,389), this was the first approval of a HER2-targeted therapeutic for NSCLC and provides new hope for patients with NSCLC who carry an activating HER2 mutation.

Like most cancer treatments, fam-trastuzumab deruxtecan-nxki can have adverse effects, some of which can be severe. One of the most concerning and, in the case of NSCLC, life threatening, is interstitial lung disease which causes stiffness in the lungs, making it difficult to breathe and get oxygen to the bloodstream. Therefore, FDA approved fam-trastuzumab deruxtecan-nxki with a warning for interstitial lung disease and recommends that patients being treated with the molecularly targeted therapeutic be monitored for signs and symptoms of interstitial lung disease, including cough, dyspnea (difficult or labored breathing), fever and other new or worsening respiratory symptoms. If interstitial lung disease is suspected, further testing and intervention must be considered.

While FDA approvals of sotorasib, adagrasib and fam-trastuzumab deruxtecan-nxki are significant advances for patients with NSCLC, all stakeholders in public health need to work together to ensure that every patient has access to and benefits from the latest developments in precision cancer medicine. Patients with lung cancer who receive molecularly targeted therapies have better survival compared to those who do not receive targeted therapies (390,391). Unfortunately, according to recent data, many patients with advanced NSCLC do not receive appropriate molecular tests or the appropriate molecularly targeted treatments due to gaps in the delivery of clinical care (392,393).

Targeting Cancers Based on a Common Genetic Feature, Not Tissue of Origin

Chromosomal translocations that involve the *RET* gene and lead to the production of activating RET fusion proteins (see **Sidebar 7**, p. 30) are rare alterations observed mostly in patients with certain types of thyroid cancer and lung cancer (394). In 2020, FDA approved the RET-targeted therapeutic, selpercatinib (Retevmo), for treating patients with metastatic NSCLC and certain thyroid cancers that test positive for chromosomal translocations involving the *RET* gene (389).

In solid tumors other than lung cancer and thyroid cancer, *RET* gene fusions are rarer, observed in less than one percent of patients (394). However, this is a distinct patient population since *RET* gene fusions are mutually exclusive of other genetic alterations and provide a unique opportunity for therapeutic intervention (394). A recent decision from FDA offers a new treatment option for these patients who until this approval had no molecularly targeted therapeutics available for their cancer.

In September 2022, FDA expanded the approval of selpercatinib for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. The approval of selpercatinib was based on the results of a phase I/II basket clinical trial (see **Figure 14**, p. 73) in which treatment with the RET-targeted therapeutic shrank tumors in nearly 44 percent of the study participants (395). Patients with a range of cancer

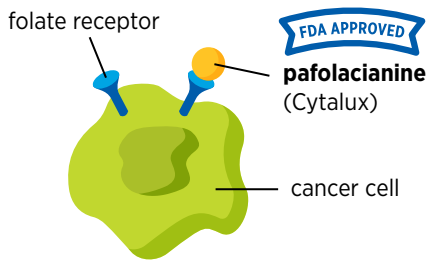
types including pancreatic adenocarcinoma, colorectal, salivary gland, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma responded to selpercatinib, emphasizing the importance of basket clinical trial designs in driving progress in precision medicine.

Delivering a Cytotoxic Drug Precisely to Ovarian Cancer Cells

In 2023, an estimated 19,710 new cases of ovarian cancer will be diagnosed in the United States, and 13,270 women will die from the disease (28). Many patients with ovarian cancer are diagnosed at an advanced stage. Patients with advanced disease are usually treated with platinum-based chemotherapeutics. Although most patients respond initially to platinum-based treatment, nearly 80 percent will experience relapse. Unfortunately, patients with recurrent ovarian cancer are resistant to platinum-based treatments and have a poor prognosis.

Folate receptor alpha (FRα) is a cell surface protein that binds to and transports folate (also known as vitamin B9) into cells. Research has shown that FRα is expressed at much higher levels in advanced ovarian cancer cells, compared to healthy adult tissues (396). There is also emerging evidence, including clinical data, that elevated FRα expression may be associated with lack of response to standard chemotherapy in ovarian cancer (397). These attributes make FRα a promising target for therapeutic intervention in ovarian cancer.

The molecularly targeted therapeutic mirvetuximab soravtansine-gynx (Elahere) targets FRα and, in November 2022, received FDA approval for adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. FDA also approved the companion diagnostic VENTANA FOLR1 RxDx Assay to identify patients eligible for the therapy.



In **November 2021**, FDA approved pafolacianine (Cytalux), the **first tumor imaging agent for ovarian cancer** that works by binding to the folate receptor, to **assist surgeons in visualizing hard to detect lesions** in adult patients during the surgery (1).

Mirvetuximab soravtansine-gynx is an antibody–drug conjugate designed to deliver a cytotoxic drug to cells that express FRα. It is the first antibody–drug conjugate to be approved by FDA to treat platinum-resistant ovarian cancer and marks the first FDA approval since 2014 for platinum chemotherapy-resistant ovarian cancer, which is associated with a poor prognosis. The approval was based on results from a phase III clinical trial that enrolled 106 patients. Nearly 32 percent of patients responded to mirvetuximab soravtansine-gynx, with a median duration of response of 6.9 months (396,397). The approval of mirvetuximab soravtansine-gynx is great news for patients, such as **Jaclyn (Jackie) Vanraaphorst**, p. 88. There is preliminary evidence that mirvetuximab soravtansine-gynx also improves overall survival for this FRα-positive ovarian cancer patient population (398).

A common adverse effect of mirvetuximab soravtansine-gynx is ocular toxicity—changes that affect the structure or function of the eye. Therefore, FDA approved mirvetuximab soravtansine-gynx with a warning that patients being treated with the molecularly targeted therapeutic be monitored and treated for signs and symptoms of vision impairment and corneal disorders.

Improving Outcomes for Patients with Metastatic Breast Cancer

Despite major advances in the treatment of breast cancer, it remains the second leading cause of cancer-related death for women in the United States (28). Recent FDA decisions have the potential to power more progress against breast cancer because they have provided new therapeutic options for certain patients with the disease.

For patients with breast cancer, one factor determining what treatment options should be considered is the presence or absence of three tumor biomarkers, estrogen and progesterone hormone receptors, which drive tumor growth upon engagement with their respective hormones, and the protein HER2. About 70 percent of breast cancers diagnosed in the United States are characterized as hormone receptor–positive and HER2-negative (3). Potential treatment options for these patients include the combination of an antihormone therapeutic such as tamoxifen, which works by preventing the hormone estrogen from attaching to its receptor; or letrozole, which works by lowering the level of estrogen in the body; or fulvestrant, which works by destroying estrogen receptors (ER) with a cyclin-dependent kinase 4/6 inhibitor. Treatment with antihormone therapeutics is also called endocrine therapy.

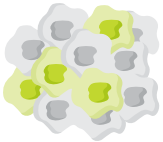
Unfortunately, most advanced, hormone receptor-positive breast cancers that initially respond to endocrine therapy eventually become treatment resistant (see **Sidebar 35**, p. 87).

SIDEBAR 35

The Challenge of Treatment Resistance

Diversity, or heterogeneity, among cancer cells within and between tumors is a major cause of treatment resistance. Some examples of heterogeneity are as follows:

Not all **cells in a tumor** may be rapidly dividing; those that are not, are **insensitive to treatments** targeting rapidly dividing cells such as cytotoxic chemotherapeutics.

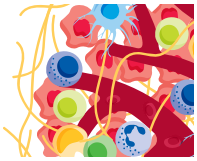


Some cancer cells in a tumor may have or may **acquire mutations** in the target of a given treatment that render the treatment ineffective in those cells and their progeny.

Some cancer cells in a tumor may have or may **acquire molecular or cellular differences** other than changes in the treatment target that render the treatment ineffective.

Redundancies among signaling pathways fueling proliferation can enable cancer cells to become resistant to a treatment even if one of the pathways is effectively blocked.

Differences in tumor microenvironment components can render a treatment ineffective.



Adapted from (67).

Resistance to fulvestrant commonly develops due to mutations in *ESR1*, the gene that encodes the ER protein. Until recently, fulvestrant was the only available FDA-approved treatment that worked by destroying ER. Therefore, patients whose tumors become resistant to it were left with limited treatment options.

The FDA approval of elacestrant (Orserdu) in January 2023 brings new hope to these patients. Elacestrant, which also works by destroying the ER, was approved for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. Unlike fulvestrant, which is delivered through intramuscular injections, elacestrant is administered orally, making it more convenient for patients to receive the treatment. The approval was based on results from a phase III, randomized clinical trial showing that among patients with ESR1 mutations, those treated with elacestrant had a 45 percent lower risk of death or disease progression than those treated with other endocrine therapies (399).

Personalizing Treatment for Patients with a Rare Solid Tumor

Rare cancer is defined by the National Cancer Institute as cancer that occurs in fewer than 15 out of 100,000 people each year. Rare cancers can be challenging for researchers to study and for physicians to treat (see **Sidebar 36**, p. 90). During the 12 months covered by this report, August 1, 2022, to July 31, 2023, the FDA approved molecularly targeted therapeutics and immunotherapeutics for treating several rare cancers, bringing the promise of precision medicine to patients, such as **Isabella (Bella) Snow Fraser**, p. 110, and **Alexis Browning**, p. 112, who often have few treatment options.

Bile duct cancer, also known as cholangiocarcinoma, is a rare but aggressive disease in which cancer arises from cells in the bile ducts. Cholangiocarcinoma is often diagnosed at an advanced stage. There are two types of bile duct cancer: intrahepatic, where cancer forms in the bile ducts inside the liver; and extrahepatic, where cancer forms in the bile ducts outside the liver. Less than 8,000 new cases of bile duct cancer are estimated to be diagnosed in the United States in 2023 and only a small number of bile duct cancers are intrahepatic (28). While rare, the incidence of intrahepatic cholangiocarcinoma is increasing worldwide (400). Surgery is the main curative treatment option for patients with intrahepatic cholangiocarcinoma. However, up to two thirds of patients have disease recurrence and patients with intrahepatic cholangiocarcinoma have a 5-year overall survival rate of less than eight percent (400).

Alterations in fibroblast growth factor receptor 2 (FGFR2), a protein involved in many cellular processes including multiplication, migration, and survival, are associated with several cancers including bile duct cancers. Nearly 14 percent of patients with intrahepatic cholangiocarcinoma have fusions or rearrangements in the *FGFR2* gene (see **Sidebar 7**, p. 30) (400). FDA had previously approved two molecularly targeted therapeutics, pemigatinib (Pemazyre) and infigratinib (Truseltiq), which block the function of FGFR2 proteins, for the treatment of patients with cholangiocarcinoma with confirmed FGFR2 fusions or rearrangements (389,401). While these agents are benefiting many patients with bile duct cancer, their efficacy has been somewhat limited due to the development of treatment resistance (400).

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"All cancer patients want one thing—extending the time that we have on this planet... And that is exactly what research is affording us."

JACLYN (JACKIE) VANRAAPHORST
Age 58 • Snoqualmie, WA

Combating Stage III Ovarian Cancer, Thanks to Research

My cancer story started with a stomachache. I was referred to a GI specialist, who ordered an ultrasound and CT scan, leading to my diagnosis of stage III ovarian cancer in 2015. Even though I have an extensive family history of cancer, this was devastating news. I was in complete shock. I underwent major surgeries to remove my uterus, cervix, ovaries, and fallopian tubes. This was followed by many rounds of chemotherapy. Over the past eight years, I have been through several types of treatments. Each controlled my cancer for a period of time, but then my CT scans and tumor marker tests would show that the cancer was back. I was basically out of options when the new drug, mirvetuximab soravtansine-gynx (Elahere), got approved by the U.S. Food and Drug Administration (FDA) in November 2022. After a series of tests to confirm that I qualified for the treatment and my insurance covered it I started taking it. Since receiving the new drug, my tumor markers have gone down significantly, and I believe that my next CT scans will confirm that it is working.

In March 2015, I started having pains in my stomach. It got to the point where one day while at a grocery store, I abandoned everything in my cart and called my doctor. Preliminary examinations did not find anything, so I decided to see a GI specialist. I had an ultrasound on a Friday, a CT scan the following Monday, and was called back to the doctor the same day. I knew that wasn't a good sign. My doctor informed me that I had ovarian cancer. I do not really remember much after that. I cried quite a bit; it was a devastating diagnosis.

Following diagnosis, I saw a gynecological oncologist who recommended a complete hysterectomy, which is major surgery that removes the uterus, ovaries, fallopian tubes, and the cervix. After surgery, I started on a chemotherapy regimen of carboplatin and Taxol and stayed cancer free for more than a year. Every three months, I received CT scans and tests for CA-125, a biomarker that can be elevated in the blood of ovarian cancer patients, to check for recurrence. One of my CT scans and CA-125 tests came back showing that the numbers were elevated. The cancer was back, and I had to go back on chemotherapy.

Over the past eight years, I have been on every possible treatment for ovarian cancer, including several types of chemotherapies, molecularly targeted therapies such as PARP inhibitors, immunotherapies, and multiple combinations of those. I would continue treatments until they became intolerable because of the toxicities or when I had a recurrence. I was starting to run out of options and doctors resorted to recycling drugs I had already tried before.

In November 2022, FDA approved a drug for ovarian cancer. I jumped through many hoops to make sure I was eligible for the drug. Fortunately, I fit all the criteria: I had received more than three prior systemic treatments including chemotherapies, and my cancer was folate receptor alpha (FRα) positive.

I started receiving Elahere in April 2023 and have been through four cycles so far. I get a CA-125 test every three weeks to monitor my cancer and it is remarkable how quickly the numbers have gone down. My CA-125 has dropped 500 points, which is amazing. I have a CT scan coming up. I hope that I get positive news and the scans show no progression—or better yet, some tumor shrinkage.

Through my experience, I have become a bigger advocate for medical research and funding. It is extremely important to continue the research and development on new therapies for all different types of cancer. Every drug I've ever been on went through a rigorous research process before receiving FDA approval. I would not be eight and a half years into what is typically a five-years-at-best prognosis if I did not have these treatments. All cancer patients want one thing—extending the time that we have on this planet. We want more time with our family, our friends, more time to do all the things that we love to do. And that is exactly what research is affording us.

Scan the QR code
to watch Jackie's video interview.

SIDEBAR 36

The Challenges Posed by Rare Cancers

Rare cancers affect fewer than 40,000 people per year in the U.S. All childhood cancers are considered rare cancers. Rare cancers pose significant challenges to patients, physicians, and researchers. According to the NCI, these challenges include:

FOR PATIENTS

Finding a physician

It is hard to find a physician who knows a lot about the rare cancer with which they have been diagnosed and how to treat it.

Treatment proximity

It is necessary to travel far to get treatment for a rare cancer.

Long diagnosis time

It takes a long time from when they first notice a symptom to the time when doctors know that the symptom is caused by a rare cancer and what type of cancer it is.

FOR PHYSICIANS

Lack of training

They have not been trained to treat a rare cancer with which their patient has been diagnosed.

Unsure expectations

They do not know what to tell their patient about what to expect with the rare cancer.

Finding expert help

They are unable to find an expert who can answer their questions about the rare cancer with which their patient has been diagnosed or identify someone to whom they can refer the patient.

FOR RESEARCHERS

Lack of information

There is no information about the rare cancer they are investigating to give ideas on how to go about tackling the disease.

Lack of research models

There are no animal or cell models of the rare cancer they are investigating in which to test their ideas.

Lack of biospecimens

There are not enough tumor samples from patients with the rare cancer they are investigating for their research.

Lack of patients

There are not enough patients with a given rare cancer to conduct a clinical trial testing a potential new treatment.

The National Cancer Institute has launched several initiatives with the goal of accelerating the pace of basic, translational, and clinical research in rare cancers. As one example, the My Pediatric and Adult Rare Tumor network (MyPART) is a group of scientists, patients, family members, advocates, and health care providers working together to find treatments for rare cancers in children, teens, and young adults faster.

In September 2022, the FDA granted approval to a third FGFR2-targeted therapeutic, futibatinib (Lytgobi) for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma that tests positive for *FGFR2* fusions or other rearrangements. The approval was based on the results of a phase I/II clinical trial that showed that futibatinib shrank tumors in 42 percent of patients (400). The median duration of response was 9.7 months. Futibatinib works differently than pemigatinib and infigratinib and preliminary data indicate that it may mitigate the challenge of treatment resistance since patients who had disease progression after prior FGFR-targeted therapy with other inhibitors maintained sustained clinical benefit with futibatinib (400).

Combining Molecularly Targeted Therapeutics to Block Tumor Growth

The BRAF enzyme has a critical role in controlling cell growth. The *BRAF* gene is altered in approximately six percent of all human cancers, including melanoma and colorectal cancer (402). Most cancer-related changes in the *BRAF* gene cause the protein to continuously stay active, thus helping cancer cells grow faster than normal cells. One of the most common cancer-related changes is the *BRAF* gene is called the BRAF V600E mutation. Presence of the BRAF V600E mutation is associated with poor outcomes for patients with certain types of cancer.

The first time FDA approved the use of two molecularly targeted therapeutics as a combination treatment for cancer was in January 2014 (67). The approval was for the use of dabrafenib (Tafinlar) and trametinib (Mekinist) for treating patients with metastatic melanoma that tests positive for activating BRAF V600E and BRAF V600K mutations. The two therapeutics target different components of the BRAF signaling pathway. Dabrafenib targets altered BRAF proteins containing V600 mutations, while trametinib targets MEK1 and MEK2, which are two proteins that mediate the function of BRAF. By blocking both BRAF and MEK, the combination therapy can more completely and effectively shut down the signaling pathway. The combination was approved after it was shown to almost double the length of time before disease progression compared with dabrafenib alone (403).

In March 2023, the same combination of molecularly targeted therapeutics was approved for pediatric patients one year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy. The FDA also approved new oral formulations of dabrafenib and trametinib for pediatric patients who are unable to swallow pills.

Brain and other nervous system tumors are the second most diagnosed cancers in children. Low-grade glioma is the most common type of pediatric brain cancer. Research has demonstrated that BRAF signaling pathway activation is common in pediatric low-grade gliomas. Therefore, the March approval of dabrafenib and trametinib combination therapy brings hope to many parents and families whose children are diagnosed with the disease. FDA approved the combination therapy based on data from a clinical trial showing that a significantly higher percentage of patients who received dabrafenib and trametinib had their tumors shrink compared to those who received the standard of care chemotherapy (47 percent vs. 11 percent, respectively) (404). Patients treated with dabrafenib and trametinib also had a 69 percent lower risk of disease progression, with a progression-free survival of 20 months, compared to seven months among patients receiving chemotherapy (404).

The FDA approval of a second combination therapy during the 12 months covered in the report provides a new and first of a kind treatment option for certain patients with colorectal cancer. The combination of tucatinib (Tukysa) and trastuzumab (Herceptin), both HER2-targeted therapeutics, was approved by FDA in January 2023 for patients with HER2-positive unresectable or metastatic colorectal cancer that has progressed following at least two standard treatments, including chemotherapy. To be eligible to receive the new combination, patients' tumors must also not have driver mutations in the *RAS* group of genes.

Colorectal cancer is the second most common cause of cancer death in the United States. An estimated 153,020 people are expected to be diagnosed with colorectal cancer in the United States in 2023 (28). Excessive production of the HER2 protein which leads to tumor cell multiplication, invasion, and metastasis is found in approximately three to five percent of patients with metastatic colorectal cancers (405) such asthat of **Brian Beck**, p. 92. The approval of the tucatinib and trastuzumab combination for this patient population was based on a phase II clinical trial which showed that 38 percent of patients who received the drug combination had their tumors shrink or disappear (406). Considering that prior treatment options for patients with HER2-positive colorectal cancer that has returned or started growing again after receiving standard treatments were not very effective, the approval of tucatinib and trastuzumab represents a significant breakthrough for this subset of patients with metastatic colorectal cancer. Ongoing studies are evaluating whether addition of tucatinib and trastuzumab to standard treatment regimens could be used earlier on as the initial treatment for metastatic HER2-positive colorectal cancer.

Adding Precision to the Treatment of Blood Cancers

Cancers that arise in blood-forming tissues, such as the bone marrow, or in cells of the immune system, are called blood cancers, or hematologic cancers. In the 12 months covered by this report, FDA has made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers (see **Sidebar 37**, p. 94).

Acute myeloid leukemia (AML) is the most commonly diagnosed leukemia in the United States, with 20,380 new cases anticipated in 2023 (28). AML has only 32 percent overall 5-year relative survival rate, the lowest among leukemias (5). Research has substantially increased our understanding of the biology of AML, in particular the different types of genetic mutations that promote AML development. This knowledge is fueling the emergence of molecularly targeted therapeutics for defined groups of patients with the disease.

One of the genes known to be mutated in about seven to 14 percent of AML cases is *IDH1* (407). Mutation in *IDHI* gene results in an altered IDH1 protein, which can drive cancer formation by interfering with normal cellular maturation and promote uncontrolled cell multiplication. This knowledge led to the development of ivosidenib (Tibsovo), the first therapeutic to target IDH1, which was approved by FDA in 2018.

In December 2022, FDA approved a second IDH1-targeted agent, olutasidenib (Rezlidhia), for adult patients with AML that has not responded to or has relapsed after other treatments, and that harbors an *IDH1* mutation as detected by an FDA-approved test. At the same time that the molecularly targeted therapeutic was approved, FDA also approved the companion diagnostic, Abbott RealTime IDH1 Assay, to identify patients with AML with an *IDH1* mutation.

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"I hope that robust funds will be allocated for future research to find ways to improve the treatments, to do more clinical trials, and to save more people."

BRIAN BECK
Age 59 • Ethridge, TN

Living with Stage IV Colon Cancer, Thanks to Clinical Trials and Research

A positive result on an in-home screening test led me to undergo a colonoscopy, which led to my diagnosis of colon cancer. I was 54. Follow-up scans revealed that the cancer had spread to my liver, which meant I had stage IV disease. I had a colon resection followed by chemotherapy and then a liver resection. This was followed by more chemotherapy. Follow-up scans showed that the cancer had recurred in my liver. At that point I participated in a clinical trial that was evaluating a combination of two immunotherapies and a molecularly targeted treatment. My cancer responded very well and, as a result, the treatments were stopped. Unfortunately, subsequent scans found new lesions. I have recently started receiving a combination of two HER2-targeted drugs, tucatinib and trastuzumab. I'm doing well, working full time, and hoping for a great response to these medicines.

When I was 54, I was encouraged by my primary care physician to get routine screening. Even though I am a health care professional and knew it was recommended to start colorectal cancer screening at age 50, I had put off my own screening. I thought I would know if there was something going on in my body, but I didn't. Positive results from an in-home, stool-based screening test led me to undergo colonoscopy, which revealed a tumor in my sigmoid colon. It was a surprise for sure. Follow-up scans showed that the cancer had metastasized to my liver.

Working with our health care team, my family and I came up with a treatment plan. I had a colon resection to remove the primary tumor. After that, I got chemotherapy and then another surgery to remove the cancer in my liver. This surgery was followed by more chemotherapy. The treatments were successful, so after a year, I stopped treatment in favor of regular monitoring scans. Unfortunately, a scan soon showed that I had a new lesion in my liver.

At that point, I joined a clinical trial that was evaluating a combination of two immune checkpoint inhibitors and a molecularly targeted therapy. I went through the same type of response: initial success, followed by a recurrence as soon as I stopped treatment. Since then, I have progressed through different treatments, including immunotherapy and others. After having another recurrence, I started on a clinical trial that is testing the combination of two HER2-targeted therapies, tucatinib and trastuzumab. I was eligible for the trial since my cancer is HER-2 positive, a pretty rare occurrence for colorectal cancer. Two weeks after I started treatment, the combination was approved by FDA. We are hoping for a great response to this combination. Maybe this will be the treatment that prevents future recurrence.

One of the things that I do now is use my story to help people who are on the fence about cancer screening, like I was. I would strongly encourage primary care and specialty clinics to make sure their patients are getting the recommended screenings. It's important to be proactive and get it done because it could save your life. I would like to thank Congress for funding the research that I have benefited from. Every treatment that I've received has been based on research. I hope that robust funds will be allocated for future research to find ways to improve the treatments, to do more clinical trials, and to save more people. I'm a testimony sitting in front of you, four and a half years into my diagnosis of stage IV cancer and still working full time. Unfortunately, that is not every patient's experience. I feel very lucky, but more people should have access to the treatments that have kept me alive. My message to Congress is that supporting research that leads to successful treatment or prevention of stage IV cancer can save future lives.

Scan the QR code
to watch Brian's video interview.

SIDEBAR 37

Recent Advances Against Blood Cancers

In the 12 months from August 1, 2022, to July 31, 2023, the U.S. Food and Drug Administration made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers, including the following:

2022

AUGUST

Myeloid/Lymphoid Neoplasm

Pemigatinib (Pemazyre), a molecularly targeted therapeutic, is approved.

OCTOBER

Multiple Myeloma

Teclistamab-cqyv (Tecvayli), a T-cell engaging bispecific antibody (a type of immunotherapeutic), is approved.

NOVEMBER

Hodgkin Lymphoma

Brentuximab vedotin (Adcetris) is a molecularly targeted therapeutic approved in combination with chemotherapeutics for patients 2 years of age and older. This is the first pediatric approval for this therapeutic.

DECEMBER

Acute Myeloid Leukemia

Olutasidenib (Rezlidhia), a molecularly targeted therapeutic, is approved.

Follicular Lymphoma

Mosunetuzumab-axgb (Lunsumio), a T-cell engaging bispecific antibody (a type of immunotherapeutic), is approved.

2023

JANUARY

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Zanubrutinib (Brukinsa), a molecularly targeted therapeutic, is approved.

Mantle Cell Lymphoma

Pirtobrutinib (Jaypirca), a molecularly targeted therapeutic, is approved.

APRIL

Stem Cell Transplant

Omidubicel-onlv (Omisirge) is a cell-based therapy approved for use in adult and pediatric patients (12 years and older) with hematologic cancers who are planned for umbilical cord blood transplantation to reduce the time to neutrophil recovery and the incidence of infection.

MAY-JUNE

Diffuse Large B-cell Lymphoma

Epcoritamab-bysp (Epkinly), a T-cell engaging bispecific antibody (a type of immunotherapeutic), is approved in May 2023.

Glofitamab-gxbm (Columvi), a T-cell engaging bispecific antibody (a type of immunotherapeutic), is approved in June 2023.

JULY

Acute Myeloid Leukemia

Quizartinib (Vanflyta), a molecularly targeted therapeutic, is approved.

Olutasidenib was approved for the treatment of AML after it was shown in a phase I/II clinical trial that 32 percent of patients treated with the molecularly targeted therapeutic had complete remission, meaning that there was no evidence of disease and full recovery of blood counts (407). Not only does the approval of olutasidenib increase treatment options for patients with IDH1-mutated AML, but there is also preliminary evidence that patients may respond longer to olutasidenib compared to the other IDHI-targeted therapy (407). A potential side effect observed among patients treated with olutasidenib is differentiation syndrome. The condition is caused by a large, rapid release of immune molecules called cytokines from leukemia cells and can lead to fever, cough, troubled breathing, build-up of excess fluid around the heart and lungs, low blood pressure, and kidney failure, but is generally readily treated with full resolution. The FDA approval is accompanied by a warning highlighting the risk of this potentially fatal adverse effect.

In July 2023, the FDA approved a second new molecularly targeted therapeutic, quizartinib (Vanflyta), for the treatment of AML. Quizartinib was approved for treating adults who have newly diagnosed AML that tests positive for a mutated *FLT3* gene known as FLT3 internal tandem duplication (ITD). Mutations in the *FLT3* gene promote the multiplication and survival of AML cells in 25 to 30 percent of cases, and patients with this type of AML have particularly poor outcomes (408). The approval was based on results from a phase III clinical trial showing that patients who received quizartinib had a 22 percent reduced risk

of death compared to those who received standard chemotherapy during the course of the clinical study (409). Quizartinib can cause several cardiac adverse effects and is therefore available only through a restricted program.

At the same time that the FDA made the decision about quizartinib, it expanded the use of the LeukoStrat CDx *FLT3* Mutation Assay as a companion diagnostic to identify patients with *FLT3* ITD mutation–positive AML who are eligible for treatment with the new molecularly targeted therapeutic.

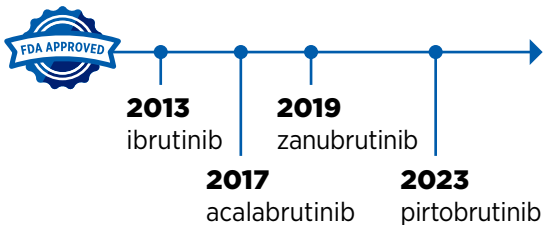
Myeloid/lymphoid neoplasm (MLN) with fibroblast growth factor receptor 1 (FGFR1) rearrangement is a rare, aggressive disease characterized by higher-than-normal levels of certain white blood cells. MLNs do not respond well to standard chemotherapy and can rapidly progress to AML (410). FGFR1 is a cell surface protein that stimulates cellular proliferation upon binding with specific extracellular molecules. In rare instances, the *FGFR1* gene fuses with another gene (an alteration known as a genetic rearrangement) resulting in a fusion protein that drives the development of MLNs.

Pemigatinib (Pemazyre) inhibits the function of FGFR1 to suppress the growth of FGFR1-driven cancers (410) and in August 2022, it was approved by FDA for adults with MLNs with *FGFR1* rearrangement who have not responded to or have relapsed after other treatments. The approval was based on results from a phase II clinical trial that showed that 79 percent of patients had a complete response to pemigatinib. Therefore, the FDA approval of pemigatinib for adult patients with relapsed or refractory MLNs with FGFR1 alteration is a major milestone for the treatment of patients who are diagnosed with the disease.

Non-Hodgkin lymphoma (NHL) is the most commonly diagnosed blood cancer in the United States. In 2023, 77,240 people in the United States are expected to be newly diagnosed with the disease (28). Notably, NHL encompasses many different types of cancer, most of which arise in immune cells called B cells. Two molecularly targeted therapeutics, recently approved by FDA for treating different subtypes of NHL arising in B cells— pirtobrutinib (Jaypirca) and zanubrutinib (Brukinsa)—target a protein called Bruton tyrosine kinase (BTK). BTK was first identified in 1993. Since its discovery, the role of BTK has been studied extensively in blood cancers and inflammatory diseases. Researchers have found that BTK is a key component of a signaling pathway that promotes the survival and expansion of NHL B cells. Consequently, BTK inhibitors have revolutionized the treatment of NHL arising in B-cells, particularly chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL) as well as certain inflammatory diseases (411).

Ibrutinib was the first BTK inhibitor approved by FDA. The approval, in 2013, was for the treatment of patients with relapsed and refractory mantle cell lymphoma (MCL). While the approval of ibrutinib was a major milestone in personalized treatment for B-cell cancers, researchers soon discovered

FDA APPROVALS OF BTK INHIBITORS FOR RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA



that in patients on continuous treatment with BTK-targeted therapy, cancer cells can acquire mutations in the *BTK* gene that render the therapeutic ineffective. Since then, newer and more sophisticated BTK inhibitors with improved specificities and thus reduced toxicities have been developed to mitigate the challenge of acquired resistance (see **Sidebar 35**, p. 87).

Pirtobrutinib (Jaypirca) is a new BTK targeted therapeutic that FDA approved in January 2023 for treating MCL. The agent was approved for patients with relapsed or refractory MCL that has not responded to or has relapsed after another treatment, including a BTK inhibitor. Pirtobrutinib has a unique mechanism of action that makes it effective even against mutated forms of BTK that are resistant to other BTK-targeted therapeutics (412). The approval of pirtobrutinib was based on results from a phase I/II clinical trial, which showed that 50 percent of MCL patients treated with the molecularly targeted therapeutic had tumor shrinkage, with 13 percent having their tumors disappear.

Zanubrutinib, another BTK-targeted therapeutic, was approved for treating patients with MCL in November 2019 (413). In January 2023, FDA approved zanubrutinib for treating adults who have CLL or SLL, which are slow-growing types of NHL. CLL and SLL are essentially the same disease but have different names depending on where in the body the NHL cells accumulate. CLL cells are found mostly in the blood and bone marrow, whereas SLL cells are found mostly in the lymph nodes.

The approval of zanubrutinib to treat CLL and SLL was based on results from two phase III clinical trials. The first trial which evaluated the efficacy of zanubrutinib in previously untreated patients with CLL/SLL showed that patients who received zanubrutinib lived a longer time without their cancer worsening compared with patients who received standard treatments. In the second trial, which compared zanubrutinib to ibrutinib in CLL/SLL patients whose disease did not respond to or came back after prior treatments, a greater percentage of patients receiving zanubrutinib were alive during the course of the study with no growth of their cancer, compared to patients taking ibrutinib (414).

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"I would tell Congress to fund cancer research as if they were funding for their family members."

COLBERT ENGLISH
Age 61 • Philadelphia, PA

Participating in Clinical Research to Make a Difference

In August 2021, I moved to South Carolina from Arkansas. Due to my heart condition, one of the first things I needed to do was to find a cardiologist. But I had to see a general practitioner so I could get a referral to a cardiologist. At that initial visit, the GP informed me I had prostate cancer.

Unfortunately, because of issues with that health care network, it was extremely difficult for me to get an appointment with a specialist, receive care, or get answers regarding my cancer diagnosis. In June 2022, I was finally able to receive a referral to a urologist. However, to see the urologist, I would have had to cancel the plan I'd made to drive cross country to celebrate my 60th birthday. Upon returning from my trip in July 2022, I ended up going to the emergency room where more blood work was done, and the ER doctor confirmed that I had prostate cancer. I saw a urologist the following Tuesday. My daughter who was with me at that appointment told me she thought I'd been rather nonchalant upon hearing my diagnosis. Cancer has been in my family. My mother died of cancer when I was 12. My oldest sister died of breast cancer. An aunt died of cancer and an older brother beat prostate cancer, so I kind of expected the diagnosis.

What I wasn't prepared for was to be told my treatment would be for the rest of my life, partially because of how long the prostate cancer went undiagnosed and untreated and partially because I couldn't be put on the traditional treatment regimen because of the medication I take for my heart condition.

The gravity of the prognosis hit me about four days later and I cried like a baby for hours. After a good cry, I then got upset that even though regular blood tests had shown that my PSA levels were increasing, I hadn't been specifically checked for prostate cancer. Nor had anyone talked to me about the risks of prostate cancer for a man of my age and ethnicity. I decided I needed to find out everything I could about this disease and what needed to be done.

My initial treatment was degarelix (Firmagon) injections. I still had questions about my diagnosis, and it was difficult to get my urologist to devote the time during my visits I needed to ask those questions. There was also a serious lack of communication with the urologist's office. I was put on an additional treatment, Xtandi, after seven months of treatment with Firmagon, but no one from the office informed me about this change. I found out because the insurance company reached out to inform me, I received approval for the new medication.

Shortly after moving to Philadelphia in March 2023, I contacted Fox Chase Cancer Center to arrange to get a second opinion. When I went in for my appointment, my doctor was prepared, and I was finally able to get some questions answered. For instance, he definitively confirmed I had stage IV cancer. He also confirmed the urologist's prognosis of my cancer being treatable but not curable. I'm happy neither of them bothered to give me an expiration date as I probably would've ignored them. I have reasons to live —specifically my daughter and my 11-year-old grandson in South Carolina and my son and my 3-year-old granddaughter here in Philadelphia.

Currently I am receiving two treatments, enzalutamide (Xtandi) and leuprolide (Lupron). The treatments are working. My last PSA test showed the values were essentially zero. However, I still hold on to the hope that one day I'll be able to stop my treatments.

I would tell Congress to fund cancer research as if they were funding for their family members. I have been part of a clinical research study at Fox Chase Cancer Center. The researchers conducting the study ask me a series of questions every 90 days. They're friendly, personable, and knowledgeable. They take the time to explain things to me, answer any questions I might have, but above all, they demonstrate that they really care. The research is aimed at better understanding prostate and other types of cancers and if they can find a cure or new treatments not just for people of color but all patients with cancer, I want to be a part of that. I want to make a difference so even if I help just one person, I will have done something and made a difference in that one individual's life.

Scan the QR code
to watch Colbert's video interview.

Blocking Progression of Metastatic Prostate Cancers

Prostate cancer is the most commonly diagnosed cancer among men living in the United States. In 2023 alone, more than 288,000 men are expected to be diagnosed with the disease (28). Research has shown that up to 30 percent of prostate cancers have mutations in genes that influence the homologous recombination repair (HRR) pathway (e.g., BRCA, ATM), a cellular process in which a group of proteins work together to repair DNA damage (415). Changes in the HRR pathway may result in the inability to repair DNA and lead to accumulation of mutations and cancer.

Poly-ADP ribose polymerase (PARP) proteins are central to a second type of DNA repair pathway called base excision repair. Researchers have found that breast, ovarian, pancreatic, and prostate cancers with genetic mutations that lead to HRR deficiency are responsive to PARP-targeted therapeutics because disruption of these two DNA repair pathways leads to pervasive DNA damage that kills cancer cells. In July 2023, FDA approved a PARP-targeted therapeutic, talazoparib (Talzenna) for treating certain groups of men with metastatic prostate cancer carrying mutations in genes that influence the homologous recombination DNA repair pathway.

Men, such as **Colbert English**, p. 96, who are diagnosed with metastatic prostate cancer are often treated initially with therapeutics that target androgens, the hormones that fuel prostate cancer growth. When the cancer stops responding to these treatments, it is referred to as castration-resistant prostate cancer. Talazoparib was approved in combination with the androgen-targeted therapeutic enzalutamide (Xtandi) for patients with HRR gene-mutated metastatic castration-resistant prostate cancer. Mutations in HRR genes such as *BRCA1*, *BRCA2*, and *ATM* were assessed prospectively using tumor tissue and/or blood-based DNA sequencing assays. The approval was based on results from a phase III clinical trial that showed that treatment with talazoparib significantly improved progression-free survival compared with treatment with enzalutamide alone (416).

Immunotherapy: Pushing the Frontier of Cancer Medicine

SPOTLIGHT

IN THIS SECTION, YOU WILL LEARN:

- Cancer immunotherapeutics work by unleashing the power of a patient's immune system to fight cancer and, over the last decade, have emerged as one of the most exciting new approaches to cancer treatment.
- Immune checkpoint inhibitors (ICIs) work by releasing the brakes on the natural cancer-fighting power of the immune system. As of July 31, 2023, the FDA has approved 11 ICIs, and there is at least one ICI approved for treating 20 cancer types and for treating any type of solid tumors that share certain molecular characteristics.
- CAR T-cell therapy provides more cancer-targeted immune cells called T cells. As of July 31, 2023, the FDA has approved six distinct CAR T-cell therapies for the treatment of a range of hematologic cancers.
- T-cell engaging bispecific antibodies work by flagging cancer cells for destruction by the immune system. As of July 31, 2023, the FDA has approved six different T-cell engaging bispecific antibodies for the treatment of many cancers, including some extremely rare cancers.
- Treatment with immunotherapeutics can lead to severe adverse effects and ongoing research is evaluating biomarkers that can identify patients who are most likely to respond to these treatments.
- The new frontier of immunotherapy, which includes preventive and therapeutic vaccines, innovative cell therapies, novel checkpoint inhibitors, and a new age of treatment combinations, is poised to transform the future of clinical cancer care.

The immune system is a complex network of cells (called white blood cells; see **Sidebar 38**, p. 100), tissues (e.g., bone marrow), organs (e.g., thymus), and the substances they make that help the body fight infections and other diseases, including cancer. The immune system actively detects threats from external (such as viruses and bacteria) and internal sources (such as abnormal or damaged cells) and works to eliminate them from the body.

The immune system is highly effective in detecting and eliminating cancer cells, a process also known as cancer immune surveillance (417). However, as cancer cells acquire new properties during the course of disease progression (see **Understanding the Path to Cancer Development**, p. 24), some cells find ways to "hide" from the immune system, such as by decreasing or eliminating the numbers and/or amounts of proteins on the surface of tumor cells that are used by the immune system to recognize cancer cells; triggering certain brakes on immune cells that prevent them from eradicating cancer cells; and releasing molecules that weaken the ability of immune cells to detect and destroy cancer cells (418). Ongoing research is focused on better understanding how tumor cells evade the immune system and leveraging this knowledge to develop additional effective cancer treatments.

Cancer Immunotherapy and How It Works

Cancer immunotherapy refers to any treatment that works by using the immune system to fight cancer. The history of invoking the immune system to treat cancer dates back to the late 19th century, when William B. Coley, a surgeon in Memorial Hospital, New York, injected bacteria into patients with inoperable malignant cancers based on his observation that an infection appeared to have the side effect of shrinking tumors. He saw excellent responses in a fraction of more than 1,000 patients with cancer he treated, and these bacterial products became known as Coley's toxins (419). The use of Coley's toxins was discontinued because of the risk of severe side effects, the emergence of radiotherapy and chemotherapy, and because scientists did not have the ability at that time to fully understand the mechanism by which they worked or failed. Over the past five decades, researchers have made unprecedented advances in understanding how the immune system detects and destroys cancer cells in the human body, which has reinvigorated the field of cancer immunology and has firmly established immunotherapy as the fifth pillar of cancer medicine (420).

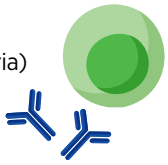
SPOTLIGHT

SIDEBAR 38

Key Cells of the Immune System

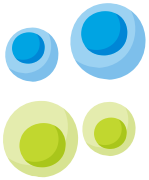
Cells of the immune system are made in the bone marrow and are called white blood cells. White blood cells work together to protect the body from external (such as pathogens) and internal (such as cancer cells) threats. Here, we briefly describe the unique functions of the white blood cells that have a central role in eliminating cancer.

B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help eliminate pathogens as well as help other components of the immune system function. Some remain as memory B cells to make the same antibody again later, if needed. Understanding of the role of B cells in eliminating cancer is growing, but the ability of these cells to make antibodies that can be used to treat patients has been harnessed for several decades.

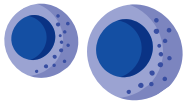


T cells help protect the body from infection and can also help fight cancer. Some remain as memory T cells to fight again later. There are two main types of T cells based on a type of protein present on their surface:

- **CD4+ T cells** help orchestrate the immune response.
- **CD8+ T cells** kill infected, damaged, and abnormal cells, including cancer cells.



Natural killer cells kill infected, damaged, and abnormal cells, including cancer cells.



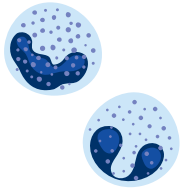
Dendritic cells educate T cells about what kinds of cells they should and should not attack.

Macrophages eat foreign materials and can ingest and fight against cancer progression, but can also make molecules that help cancers grow.

Mast cells release chemicals against pathogens and stimulate the immune system but can also provide factors that aid tumor growth and spread.

Neutrophils are among the first immune cells to respond to external and internal threats, releasing chemicals that fight pathogens and stimulate the immune system. The effects of these cells can either fight against cancer progression or potentially help cancers grow.

Basophils and **eosinophils** release chemicals against pathogens and stimulate the immune system. The effects of these cells can either help cancers grow or fight against cancer progression.



Adapted from (9).

COLEY'S TOXINS

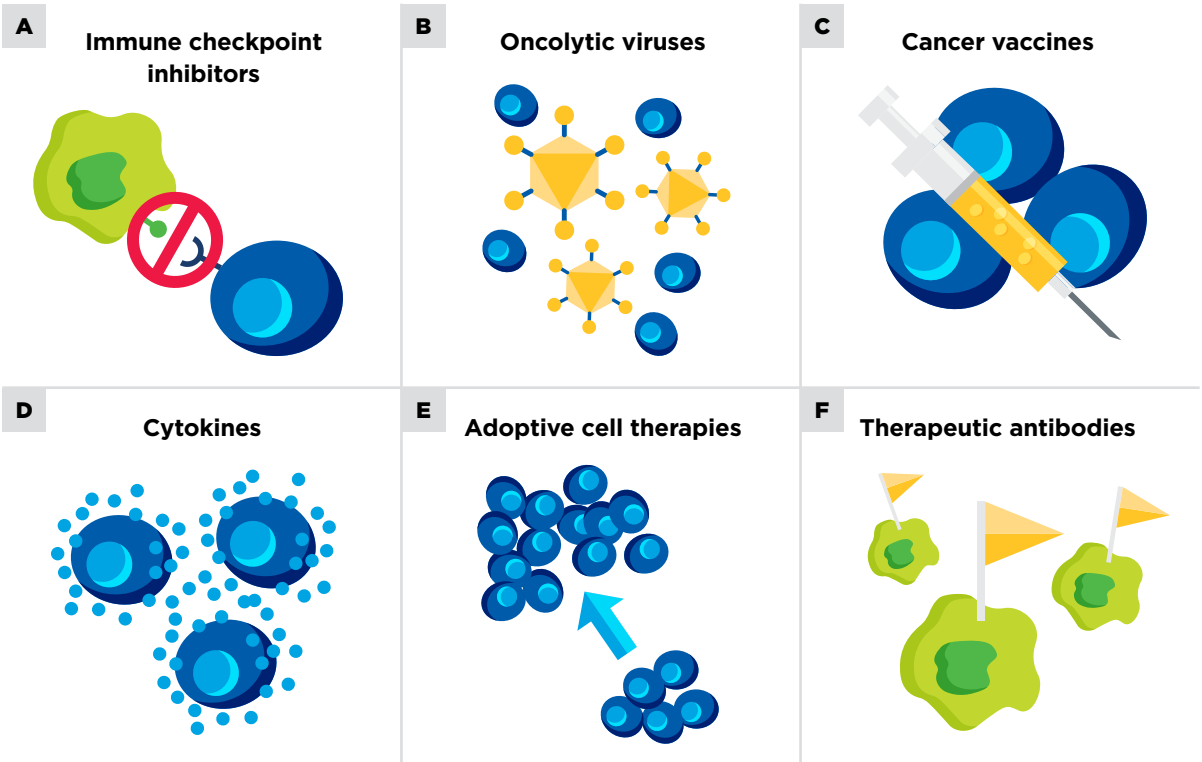
Coley's toxins, **widely considered one of the first examples of immunotherapy**, are a **mixture of toxins** collected **from certain types of bacteria**. The mixture is named after William B. Coley, a surgeon at Memorial Hospital, New York, who developed the toxins in the late 19th century as a treatment for cancer (419).

Groundbreaking basic research in the field of immunology—the study of the immune system—has laid the foundation of modern immunotherapy, one of the most exciting new areas of cancer treatment along with molecularly targeted therapeutics (see **Figure 15**, p. 76). Cancer immunotherapeutics leverage the natural ability of the immune system to fight cancer (see **Figure 17**, p. 101) (421). There are various ways in which different immunotherapeutics unleash the immune system to fight cancer.

Some immunotherapeutics work by unleashing the natural cancer-fighting powers of the immune system. Immune checkpoint inhibitors (ICIs) are examples of immunotherapeutics that work in this way. ICIs have revolutionized the landscape of cancer treatment and, over the past decade, have been approved widely by FDA for use in the treatment of diverse cancer types (see **Releasing the Brakes on the Immune System**, p. 101). Some immunotherapeutics dramatically amplify the cancer killing power of the immune system by either providing more

FIGURE 17

Immunotherapeutics Can Work in Many Ways



Decades of research and technological advances have allowed researchers to harness the potential of the immune system in treating cancer. In just over a decade, FDA has approved different types of immunotherapeutics that work in multiple ways. These include immunotherapeutics that unleash the natural killing power of the immune system to treat cancer by releasing the brakes on the immune system, such as immune checkpoint inhibitors (A); immunotherapeutics that comprise a virus that preferentially infects and kills cancer cells by releasing molecules that trigger cancer-fighting T cells (B); immunotherapeutics that amplify the cancer killing ability of the immune system, such as CAR T-cell therapy (C); immunotherapeutics that enhance the function of the immune system, such as cytokines (D); immunotherapeutics that provide more cancer-targeted immune cells to enhance the killing power of the immune system (E); and immunotherapeutics that flag cancer cells for destruction by the immune system, such as therapeutic antibodies. (F).

cancer-targeted immune cells (see **Adoptive Cell Therapy**, p. 109), or by enhancing T-cell function utilizing proteins known as cytokines (see **Enhancing Immune Cell Function**, p. 117) or cells that trigger cancer-fighting T cells (e.g., the cancer vaccine sipuleucel-T or Provenge).

Other immunotherapeutics work by flagging cancer cells for rapid destruction by the immune system. These include therapeutic antibodies that work by bringing immune cells into close contact with cancer cells and activating them, which leads to cancer cell destruction (422) (see **Directing the Immune System to Cancer Cells**, p. 120).

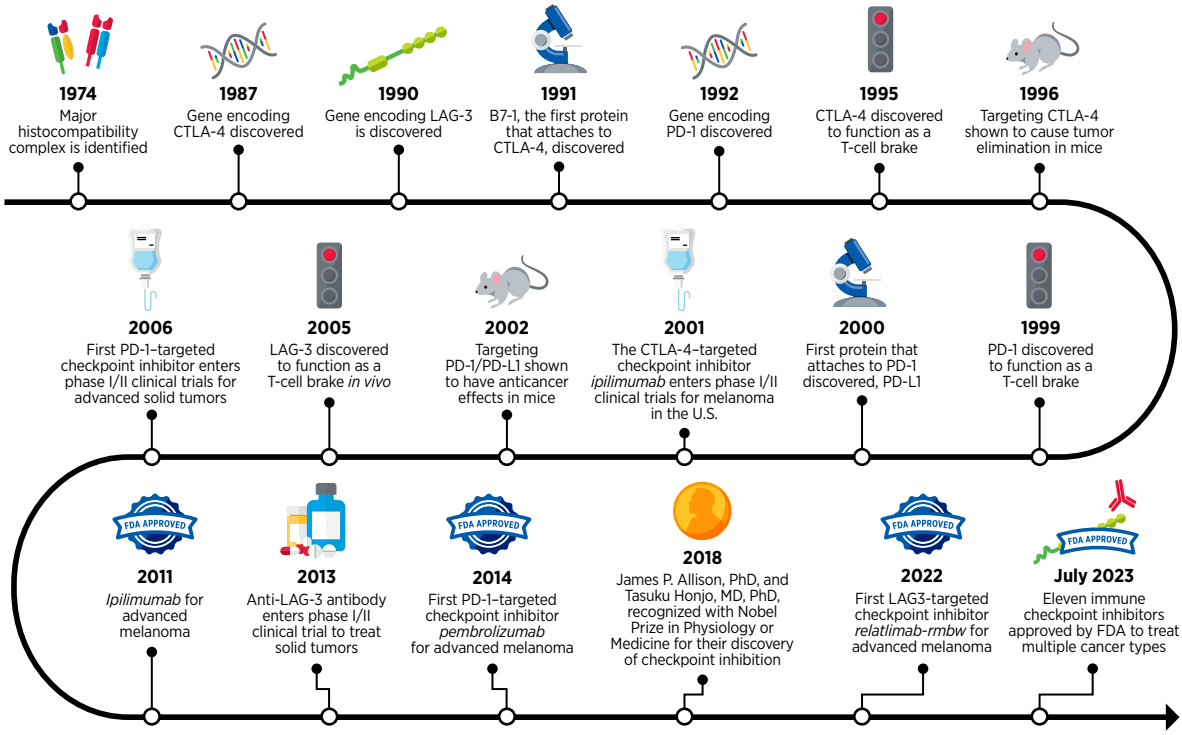
Yet other immunotherapeutics comprise a virus that preferentially infects and kills cancer cells, releasing molecules that trigger cancer-fighting T cells; these are called oncolytic virotherapeutics, for example, talimogene laherparepvec (T-Vec; Imlygic).

Releasing the Brakes on the Immune System

Decades of research have revealed that some tumor cells have increased levels of certain proteins on their surface that attach to and activate "brakes" on T cells, thus stopping them from attacking cancer cells. These brakes are proteins on the surface of T cells and are called immune checkpoint proteins. Immune checkpoint inhibitors (ICIs) are a class of transformative new therapeutics that can release the brakes on T cells and trigger T cells to destroy cancer cells (423).

FIGURE 18

Decades of Research Breakthroughs Along the Way to Developing Immune Checkpoint Inhibitors



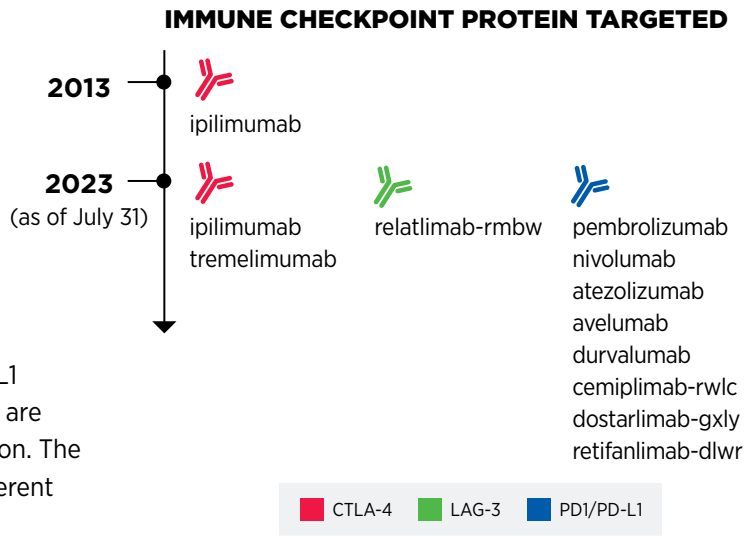
Immune checkpoint inhibitors (ICIs) are cancer immunotherapeutics that work by releasing certain "brakes" called immune checkpoint proteins on the surface of cancer-fighting immune cells. The first ICI to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab, in March 2011. Ipilimumab targets an immune checkpoint protein on T cells called CTLA-4. Tremelimumab—the only other ICI that works similarly—was approved in October 2022. Several other ICIs target a second immune checkpoint protein called PD-1 and its binding partner, a protein called PD-L1. The first of these immunotherapeutics to be approved by FDA was pembrolizumab, in September 2014, and retifanlimab-dlwr—the newest member of this class of immunotherapeutics—was approved in March 2023. Yet another checkpoint protein, called LAG-3, is the target of relatlimab-rmbw, an ICI that was approved by FDA in March 2022. Decades of basic, translational, and clinical research underpinned the development of ipilimumab, pembrolizumab, and relatlimab-rmbw, starting with the discoveries of the CTLA-4, LAG-3, and PD-1 genes in 1987, 1990, and 1992, respectively. Other milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4, LAG-3, and PD-1, the identification of binding partners that attach to and trigger the brake function, and the demonstration that ICIs targeting these brakes can prevent them from being triggered. While all the ICIs currently approved by FDA work on brakes located on T cells, ongoing research is evaluating the clinical utility of targeting brakes on additional immune cell types.

Adapted from (163).

The story of ICIs began in 1987, when researchers discovered a gene that they called CTLA-4 (see **Figure 18**, p. 102) (424). However, it took nearly eight years before the immune checkpoint function of CTLA-4 was discovered, and another 16 years of basic and clinical research before this knowledge was translated into a clinically effective therapy, a therapeutic antibody that targets CTLA-4, ipilimumab (Yervoy). Upon attaching to CTLA-4 on the surface of patients' T cells, ipilimumab releases a set of brakes on T cells, spurring them into action. Ipilimumab was the first treatment in history to improve survival for patients with metastatic melanoma and was approved by FDA for this use in March 2011.

Changing the landscape of FDA-approved immune checkpoint inhibitors

- In 2022, 1,236 new clinical studies were initiated, globally, testing PD-1/PD-L1 targeted immune checkpoint inhibitors in cancer, a 54 percent increase from 2017 (332).
- There are >3,000 ongoing clinical studies, worldwide, testing PD-1/PD-L1 inhibitors; >80 percent of these trials are evaluating these agents in combination. The combination agents target >300 different pathways (332).



Motivated by the success of ipilimumab and the need to provide new treatment options for patients who did not achieve long-term response to ipilimumab, researchers focused on targeting a second checkpoint protein, PD-1, as well as one of the proteins that attaches to it, PD-L1. The first FDA approval of an ICI targeting PD-1 or PD-L1 occurred in September 2014, when pembrolizumab (Keytruda), which targets PD-1, was approved for treating certain patients with metastatic melanoma. Notably, since the approval of pembrolizumab, three additional ICIs have been approved by FDA for the treatment of patients with metastatic melanoma, to be used alone or in combination with another ICI or molecularly targeted therapeutics. Thanks to these clinical breakthroughs, mortality from melanoma has declined significantly, for the first time in four decades, during the period between 2013 and 2017, and continues to trend downward (425).

The third immune checkpoint protein targeted by an ICI is LAG-3. The first and, so far, only LAG-3 targeted ICI, relatlimab-rmbw, was approved by FDA in March 2022 in combination with nivolumab (Opdualag) for treatment of certain patients with melanoma.

Two researchers whose pioneering work established the field of ICIs, **James P. Allison, PhD**, p. 104, and Tasuku Honjo, MD, PhD, were recognized with the 2018 Nobel Prize in Physiology or Medicine for "their discovery of cancer therapy by inhibition of negative immune regulation."

The use of ICIs in the treatment of cancer has rapidly expanded over the last decade and these therapeutics are considered one of the most exciting approaches to cancer treatment. This is in part because some patients with metastatic disease who have been treated with these therapeutics have had remarkable and durable responses. As one example, long-term results from a clinical trial testing the ICI pembrolizumab for patients with advanced NSCLC showed that 23 percent lived 5 or more years, which stands in stark contrast to the historical 5-year relative survival rate for patients with advanced NSCLC of about 5 percent (426). Recent analysis suggests that the use of ICIs is also favorably associated with patients' quality of life (427).

As of July 31, 2023, FDA has approved eleven ICIs, targeting one of three different T-cell brakes, CTLA-4, PD-1/PD-L1, or LAG-3. Notably, these groundbreaking treatments are FDA approved for an increasingly broad array of cancer types (see **Figure 19**, p. 106). As of July 31, 2023, there was at least one checkpoint inhibitor approved for treating 20 cancer types and for treating any type of solid tumor characterized by the presence of either of three specific molecular characteristics (see **Figure 19**, p. 106).

A watershed moment in cancer medicine was the May 2017 FDA approval of the ICI pembrolizumab for treatment of patients with solid tumors not of a specific organ/tissue type but rather characterized by the presence of either of two specific molecular characteristics, or biomarkers, called microsatellite instability–high and DNA mismatch–repair deficiency. These biomarkers are found in a small proportion of cancers arising at numerous sites in the body, including the colon, endometrium, stomach, and rectum. This was the first ever approval of a therapeutic to treat cancer based solely on its molecular alterations rather than the site of origin. It was also an example of precision immunotherapy, whereby a patient's immunotherapy is tailored to the molecular characteristics of his or her tumor. Remarkable progress in our understanding of cancer biology and in the conduct of clinical research led to this approval. Since 2017, pembrolizumab has been approved for the treatment of patients with tumors characterized by another biomarker known as high tumor mutational burden (TMB); additionally, a second ICI, dostarlimab-gxly, and several molecularly targeted therapeutics have received site-agnostic FDA approvals based on biomarkers and are providing new treatment options and new hope to patients with a wide range of cancer types.

continued on page 106

Looking to the Future of Immunology

James P. Allison, PhD, FAACR
2018 Nobel Laureate in Physiology or Medicine
Vice President, Immunobiology; Chair, Department of Immunology; Executive Director, Immunotherapy Platform; Director, James P Allison Institute; Olga Keith Weiss Distinguished University Chair for Cancer Research
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Immunotherapy has emerged in the last decade alongside surgery, chemotherapy, radiation, and targeted therapy as a pillar of cancer therapy. Notably, immune checkpoint therapy (ICT) agents against the T cell checkpoints CTLA-4 and PD-1/PD-L1 have provided long-term remissions against previously intractable cancers, such as metastatic melanoma and lung cancer. The combination of the two provides an even higher response rate and is now FDA approved as a standard of care. Since anti-CTLA-4 and anti-PD-1/PD-L1 antibodies globally unleash T cell responses, they are not specific for a given tumor type, and clinical data indicate responses against a wide range of cancers, including renal cell carcinoma, lung cancer, bladder cancer, hepatocellular carcinoma, and many others. These immunotherapy agents drive diverse immune responses and enable formation of antigen-specific memory responses, thereby providing a "living drug" with the capability to eliminate the tumor indefinitely. Both anti-CTLA-4 and anti-PD-1/PD-L1 agents have been FDA approved as monotherapy and as combination therapies, including combinations with chemotherapy and targeted therapies such as tyrosine kinase inhibitors (TKIs). Most recently, another immune checkpoint agent, anti-LAG-3, was approved in combination with anti-PD-1 for the treatment of patients with metastatic melanoma revealing that there are additional inhibitory receptors that can be blocked for therapeutic benefit.

Whereas ICT provides lasting remissions to some patients with specific cancers, many patients do not respond to treatment. Cancers with few immune cells in the tumor such as pancreatic cancer and glioblastoma generally do not respond. In addition, other immunosuppressive

elements in the tumor microenvironment (TME), found on both immune and nonimmune cells, may lead to resistance to ICT. Efforts to unleash the immune response directly at the level of the T cell may be largely saturated as CTLA-4 and PD-1 appear to act at the beginning and end of the T cell activation process. A combinatorial therapy approach that also targets other aspects of the complex tumor-immune interactions in the TME offers increased promise to expand ICT benefit to all patients and overcome acquired resistance.

Clinical trials of immunotherapy combinations against a wider range of cancers have been hampered by the number of potential combinations, a limited patient pool, and our still restricted knowledge of immune regulatory networks within the tumor. A more complete understanding of the immune system and how it is affected by cancer therapies is also necessary to guide the development of more effective, rationally designed immunotherapy combinations. In addition, multiple ongoing research studies and clinical trials include efforts to unravel the complex interplay between immune responses and specific tumor processes, with hopes of identifying biomarkers that define specific subsets of patients more likely to respond to specific immunotherapy combinations. Many of these efforts are being performed in the metastatic disease setting; however, there have been promising data to indicate that ICT can also provide significant benefit in earlier stages of disease, and neoadjuvant treatment with ICT will clearly be an area of future FDA approvals.

Our group conducted the first neoadjuvant clinical trials with ICT, which consisted of anti-CTLA-4 therapy prior to surgery for patients with localized bladder cancer and prostate cancer. These studies not only provided safety data for the use of ICT in the neoadjuvant setting, but also analysis of the resected tumor demonstrated changes in immune responses that occur in the tumor microenvironment as a result of ICT. More recently, in a randomized phase 2 clinical trial with melanoma patients who received anti-PD-1 prior to surgery (neoadjuvant therapy), as compared to treatment after surgery (adjuvant therapy), clinical outcomes were better in patients who received the neoadjuvant therapy. These data fit with the observation that ICT is more effective earlier in treatment when the immune system has a greater chance of encountering tumor antigens and initiating a response. Furthermore, neoadjuvant immunotherapy in select subsets of patients has the potential to eliminate tumors such that patients will not need additional treatments such as chemotherapy, radiation, or even surgery. In a study with rectal cancer patients who had mismatch repair defects in their tumors, anti-PD-1 neoadjuvant therapy led to complete responses with elimination of all tumors in 12 patients. These patients not only did not need to undergo additional treatments with chemotherapy and radiation therapy, but remarkably also did not need to undergo surgery. These data highlight the importance of biomarkers (in this case the evidence of mismatch repair defects) to select appropriate patients and the power of immunotherapy to revolutionize cancer treatment.

Realization of the full promise of cancer immunotherapy lies in the accumulation and integration of a wide range of data, incorporation of multiple immune responses, addressing tumor-specific factors, and inclusion of patient-specific history, including data such as the use of antibiotics or microbiome data. Given the large number of ongoing clinical trials, we need to adopt a "reverse translational approach" and invest in obtaining longitudinal samples from patients for assessing evolving immune responses, tumor microenvironment, and host factors. Immune profiling of pretreatment and on-treatment longitudinal biopsy samples from patients can provide critical information about changes in relevant targets in defined patient cohorts. These targets can then be evaluated and therapeutic opportunities validated in animal models, which can guide rational combination therapy strategies in future clinical trials. The "reverse translational model" will require access to patients, the ability to gather relevant data (genomic, epigenomic, transcriptomic, spatial, microbiome, phenotypic) at scale, a strong data science program, discovery science that can answer the questions that arise from immune profiling, and the ability to initiate or guide therapeutic development programs.

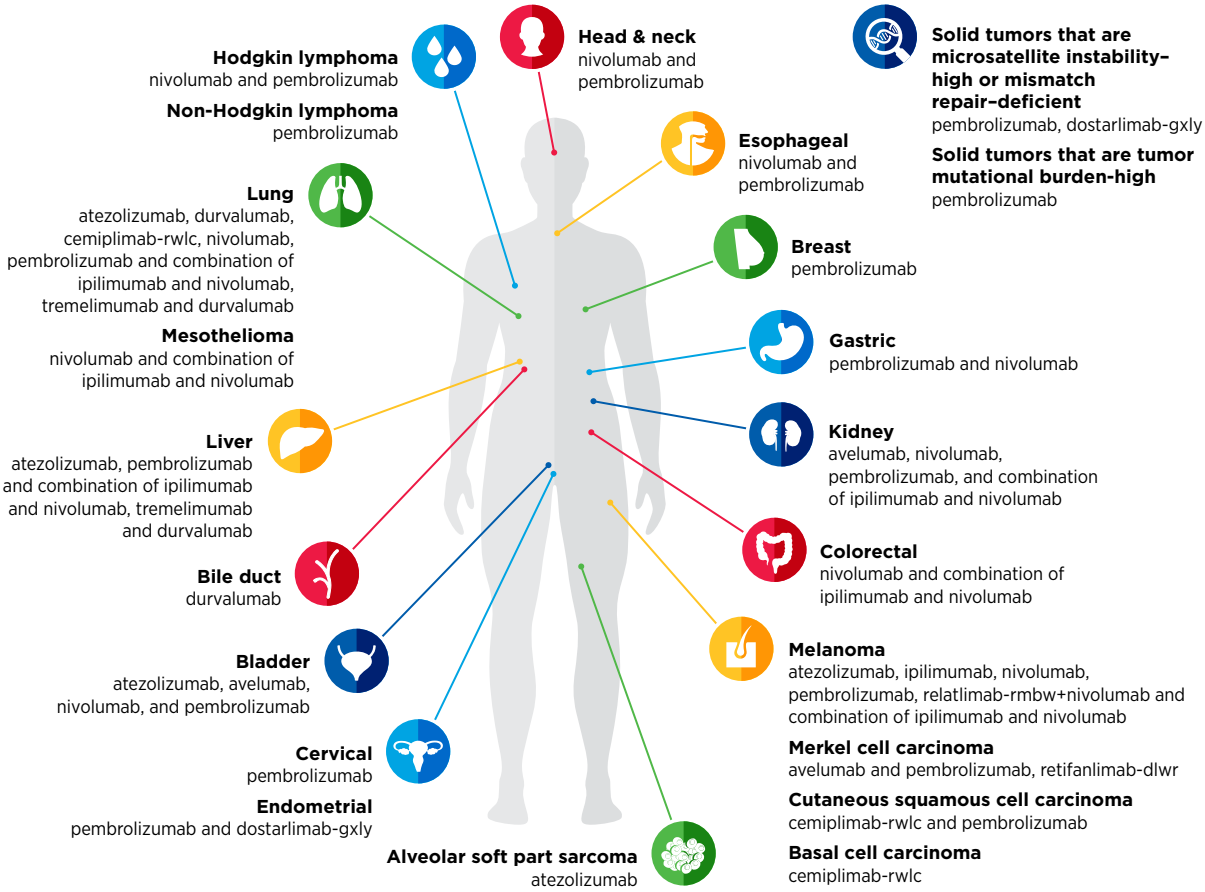
The goal is to accelerate the path of new drugs and drug combinations to the clinic. By bringing clinical trials, immune profiling, discovery science, data science, and drug development together on a coordinated team, we can make this vision a reality. Such an ambitious undertaking requires the strong and continuous support of academic institutions with large research teams, generous funding sources, efficient regulatory teams to effectively open and monitor new clinical trials, and pharmaceutical partners, but the benefits should be enormous.

SPOTLIGHT

FIGURE 19

Going Deep with Immune Checkpoint Inhibitors

FDA-APPROVED AS OF 2023



Immune checkpoint inhibitors (ICIs) are cancer immunotherapeutics that work by releasing certain "brakes" on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. The first ICI to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Three-and-a-half years passed before the second ICI was approved, pembrolizumab (Keytruda), also for metastatic melanoma. Since then, nine additional ICIs have been approved by FDA. In addition, FDA has expanded the number of cancer types for which there is at least one ICI approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of July 31, 2023, there was at least one ICI approved for treating 20 cancer types and for treating any type of solid tumor characterized by the presence of specific molecular characteristics. In addition, with many ICIs approved for treating multiple cancer types, there are several diseases for which there is a deep selection of ICIs available as a treatment option.

Adapted from (1).

During the 12 months spanning this report, August 1, 2022, to July 31, 2023, FDA approved two new ICIs for the first time—tremelimumab (Imjudo) and retifanlimab-dlwr (Zynyz)—and expanded the uses of two of the previously approved ICIs—durvalumab (Imfinzi) and atezolizumab (Tecentriq)—to treat additional types of cancer.

In October 2022, tremelimumab (Imjudo) became the tenth ICI to be approved by FDA. It was approved in combination with another ICI, durvalumab (Imfinzi), for treating adult patients with hepatocellular carcinoma (HCC, a type of liver cancer) whose tumor is not removable with surgery. Tremelimumab is the second FDA-approved ICI that targets the checkpoint protein CTLA-4, while durvalumab blocks the checkpoint

protein PD-L1. Combined targeting of the two checkpoints, CTLA-4 and PD-1/PD-L1, has shown clinical benefit in a number of cancer types.

HCC is the most commonly diagnosed liver cancer in adults and the third leading cause of cancer-related deaths worldwide (428). Most HCC cases are diagnosed at an advanced stage when surgical removal is not an option, and many patients experience cancer recurrence after initial treatment (429). Patients with HCC that is not removable surgically are treated with systemic therapy, including anti-angiogenic treatments that block the development of blood vessels or with ICIs, often as combination therapy. While these treatments have led to some improvement in survival for patients with HCC not surgically removable, additional treatment options are needed for this globally diverse patient population, highlighting the importance of FDA approval of the tremelimumab and durvalumab combination.

The efficacy of tremelimumab plus durvalumab was tested in a randomized, phase III clinical trial in patients with unresectable HCC who had not received prior systemic treatment. The study compared the efficacy of tremelimumab plus durvalumab to the standard of care, which is treatment with the molecularly targeted antiangiogenic therapeutic sorafenib (Nexavar). Findings from the trial showed that patients who received the ICI combination experienced a 22 percent reduction in the risk of death during the course of the study compared to patients who received sorafenib (429).

In the 12 months covered in this report, FDA also expanded the approval of the tremelimumab and durvalumab combination for certain patients with lung cancer. In November 2022, FDA approved tremelimumab in combination with durvalumab and platinum-based chemotherapy for treatment of adult patients with metastatic NSCLC whose tumors do not have mutations in the *EGFR* or *ALK* genes. Patients with NSCLC with tumors that have alterations in *EGFR* or *ALK* are usually treated with molecularly targeted therapeutics that specifically target the EGFR or ALK proteins.

The approval was based on results from a phase III randomized clinical trial that compared the efficacy of the tremelimumab, durvalumab, and chemotherapy combination to chemotherapy alone, among patients with NSCLC who had not received prior systemic treatment. The data from the clinical trial showed that patients receiving the ICI combination experienced a 23 percent reduction in the risk of death during the course of the trial compared to those receiving chemotherapy alone (430). The median overall survival (see **Sidebar 32**, p. 80) was 14 months in patients treated with the combination versus 11.7 months in patients treated with chemotherapy alone (430).

According to the National Cancer Institute, a **locally advanced cancer** is one that **has spread** from where it started **to nearby tissue or lymph nodes**.

In September 2022, FDA approved durvalumab in combination with the chemotherapeutics gemcitabine and cisplatin for adult patients with locally advanced or metastatic cancer of the biliary tract.

Biliary tract cancers include various rare but aggressive epithelial malignancies (see **Sidebar 5**, p. 26), including bile duct cancer and gallbladder cancer, among others and account for three percent of all gastrointestinal cancers. Surgical removal of the entire tumor is currently the only curative treatment for biliary tract cancer. Unfortunately, many patients are diagnosed at an advanced stage when surgery is no longer an option. For over a decade, the combination of gemcitabine and cisplatin has remained the standard initial treatment for patients with advanced biliary tract cancer, including those whose cancer returned after the initial treatment.

Research has shown that the tumor microenvironment of biliary tract cancers may suppress the immune system, indicating that there may be limited benefit from immunotherapeutics, if used alone. Chemotherapeutics are known to modulate the immune system, leading researchers to hypothesize that a combination of ICIs with chemotherapy could improve response to immunotherapy. Recent data from two clinical trials supported this hypothesis and showed that patients with advanced biliary tract cancer benefit when ICIs such as durvalumab or pembrolizumab are administered as a combination with gemcitabine and cisplatin (431,432). One of these trials provided the basis for the approval of durvalumab in biliary tract cancer.

The study, a phase III randomized clinical trial, found that adding durvalumab to standard chemotherapy modestly extended how long patients with advanced biliary tract cancer lived (431). The FDA approval was based on the fact that patients who received chemotherapy plus durvalumab had a 20 percent reduction in the risk of death during the course of the trial compared to patients who received chemotherapy alone (431). While these data offer hope for patients with a very aggressive disease, there is urgent need for continued research to identify more effective treatments for this difficult-to-treat group of cancers.

In addition to combinations with other ICIs, researchers are combining ICIs with molecularly targeted therapeutics to maximize the potential of precision medicine. As one example, in April 2023, FDA approved a combination of a molecularly targeted therapeutic, called enfortumab vedotin-ejfv (Padcev) and pembrolizumab to treat patients with bladder cancer. The approval was based on findings of a clinical study that showed

that 73 percent of the treated patients responded to the drug combination and the response lasted, on average, for 22 months (433), bringing hope to patients with bladder cancer who otherwise have limited treatment options available.

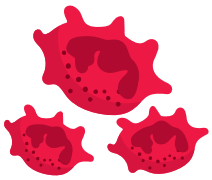
Research has shown that up to 60 percent of bladder cancers are characterized by elevated levels of a protein called nectin-4 (434). Enfortumab-vedotin-ejfv is an antibody–drug conjugate that comprises a cytotoxic agent, monomethyl auristatin E, attached by a linker to a nectin-4–targeted antibody. When the antibody attaches to nectin-4 on the surface of bladder cancer cells, the antibody–drug conjugate is internalized by the cells, which leads to release of monomethyl auristatin E from the linker and antibody. Once free, monomethyl auristatin is toxic to cancer cells.

One of the new cancer types for which an ICI is now an approved treatment option is alveolar soft part sarcoma (ASPS). In December 2022, FDA approved the ICI atezolizumab (Tecentriq) for the treatment of adult and pediatric patients two years and older with ASPS that has spread to other parts of the body or cannot be removed by surgery.

Alveolar soft part sarcoma is an extremely rare cancer that mainly affects adolescents and young adults, such as **Isabella (Bella) Snow Fraser**, p. 110 and **Alexis Browning**, p. 112. According to NCI, about 80 people are diagnosed with the disease in the United States each year. ASPS is a slow-growing cancer that forms in soft tissues such as muscle, fat, or nerves. Although the disease grows slowly, once metastatic, ASPS has poor outcomes. Chemotherapeutics have limited benefit and molecularly targeted therapeutics do not have lasting effectiveness against ASPS.

Atezolizumab is a PD-L1-targeting ICI that has been approved previously for the treatment of patients with several cancer types, including liver cancer, melanoma, and lung cancer (see **Figure 19**, p. 106). The new FDA approval was based on data from a phase II clinical trial showing that about a quarter of the patients with ASPS responded to atezolizumab with some tumor shrinkage. Among patients who responded to the treatment, 67 percent had a response lasting at least six months, and 42 percent had a response lasting at least 12 months. The approval represents a significant advance for a rare disease as well as for pediatric patients with cancer, two research areas that require more intensive attention for continued progress.

Merkel cell carcinoma is a **rare and aggressive form of skin cancer** with a **high risk for recurrence and metastasis**. Researchers estimate that the current number of 3,000 new cases per year will increase to >3,250 cases per year by 2025 (435).



In March 2023, retifanlimab-dlwr (Zynyz) became the second new ICI approved by FDA during the 12 months covered by the report. It was approved for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma, a rare and aggressive form of skin cancer. Retifanlimab-dlwr targets the PD-1 brake on the surface of T cells, preventing T cells from attaching to the cells that can trigger the brake and deactivate them. The approval was based on the finding that treatment with retifanlimab-dlwr resulted in tumor shrinkage in more than half of the patients who received the treatment as part of a phase II clinical study. With this decision, retifanlimab-dlwr became the third ICI approved by the FDA for Merkel cell carcinoma (see **Figure 19**, p. 106).

Immune checkpoint inhibitors have yielded extraordinary benefit for many patients, but they can have adverse effects (see **Current Challenges in Cancer Immunotherapy**, p. 125) particularly the induction of autoimmune-like conditions. This occurs because ICIs not only release the brake on cancer fighting immune cells but also some that recognize and injure normal tissues. To predict which patients are likely to experience adverse events and design treatments to combat these events without compromising the anticancer efficacy of the ICI, researchers must better understand why and how the adverse effects arise. This is an area of extensive research investigation. Another important area of scientific inquiry is to identify behavioral and clinical factors, such as diet, physical activity, gut microbiome composition, and optimal combinations with other therapeutic modalities that can boost the efficacy of ICIs and increase the number of patients who respond favorably to these lifesaving treatments.

As documented in this report and in the past 12 editions of the *AACR Cancer Progress Report*, ICIs have transformed the clinical care of patients with a diverse array of cancer types including historically intractable diseases such as metastatic melanoma, lung cancer, and kidney cancer (436). While their use was initially limited to people with very advanced cancers that were no longer responding to standard treatments, checkpoint inhibitors are increasingly being approved as first-line—initial—treatments for patients. Recent data show that compared to the current standard treatments such as chemotherapy, ICI use in the first-line setting may improve survival for certain patients (437-439).

Researchers are also evaluating how to best integrate the use of ICIs along with standard treatments such as surgery, radiation therapy, and/or chemotherapy in patients with early-stage cancer (440,441). One area of extensive research is the use of these therapeutics before initial surgery, known as neoadjuvant treatment, in people with locally advanced cancers that are largely restricted to their original location. The first neoadjuvant clinical trial with ICI was conducted in 2006, which provided the first safety

data and evidence of clinical efficacy for ICI in the neoadjuvant setting (442,443). These critical data set the stage for additional neoadjuvant clinical trials with ICI. Based on such studies FDA has approved the ICIs pembrolizumab and nivolumab as neoadjuvant treatments for patients with triple-negative breast cancer and lung cancer, respectively, that are diagnosed at an early stage.

The immense benefit of ICIs as neoadjuvant therapy was highlighted in two recent clinical trials conducted in patients with early-stage colorectal cancer that has specific genetic characteristics. Neoadjuvant treatment with either of the ICIs pembrolizumab or dostarlimab yielded remarkable responses, with some patients not even needing surgery and showing no evidence of cancer for years following the ICI therapy (444,445). A similar benefit of neoadjuvant ICI therapy has been noted in patients with melanoma, and those with cutaneous squamous cell carcinoma—the second most common type of skin cancer diagnosed in the United States—among other diseases (446,447).

Collectively, these results highlight a paradigm shift in the treatment of early-stage cancers, with researchers hypothesizing that ICI therapy alone may eliminate cancers for certain patients without the need for any further treatments. While these data bring new hope to the cancer community, before such approaches to ICI use can become standard of care, it is important that they are shown in rigorous, well-designed, large clinical trials to prevent/delay cancer recurrence and improve how long patients live. Ongoing research and future efforts will identify optimal biomarkers for determining patients who would most benefit from such novel ICI regimens.

Boosting the Cancer-killing Power of Immune Cells

Research has shown that immune cells, such as T cells, are naturally capable of destroying cancer cells. It has also shown that in patients with cancer, there are often insufficient numbers of cancer-killing T cells, and that the cancer-killing T cells that are present are unable to find or destroy the cancer cells for one of several reasons. This knowledge has led researchers to identify several ways to boost the ability of T cells to eliminate cancer cells.

Adoptive Cell Therapy

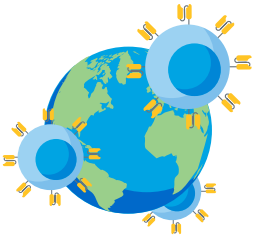
Adoptive cell therapy (ACT), also called cellular immunotherapy, is designed to dramatically increase the number of cancer-killing immune cells a patient has, thereby boosting the immune system's ability to seek and destroy cancer cells (448). While many of the adoptive cell therapies currently in late-stage clinical development and all that are approved by FDA utilize patient-derived T cells (see **Sidebar 39**, p. 116), ongoing research is looking to harness the cancer killing power of other immune cell types including natural killer (NK) cells and macrophages, among others (see **A New Wave of Adoptive Cell Therapeutics**, p. 129). Chimeric antigen receptor (CAR) T-cell therapy is one type of ACT that has generated enormous excitement in cancer medicine in recent years. This is because treatment with CAR T cells has demonstrated unprecedented efficacy in certain patients with very advanced leukemia or lymphoma.

Like ICIs, CAR T-cell therapy is the culmination of decades of basic, translational, and clinical research utilizing knowledge of the cellular and molecular components of the immune system, genetic engineering, and the biological underpinnings of blood cancers. The concept of a synthetic receptor was first reported in the late 1980s when researchers showed that the engineered proteins could be introduced into T cells and upon binding with appropriate partners could activate T cells, leading to killing of cancer cells (449). These discoveries, along with scientific breakthroughs in the 1990s on ways to expand T cells in large numbers in the laboratory and return them to the body where they could attack cancer cells, laid the foundation for the first clinical studies in the early 2010s that evaluated CAR T-cell therapy in patients with advanced leukemia (450-452).

In 2017, tisagenlecleucel (Kymriah) became the first FDA approved CAR T-cell therapy when it was approved for the treatment of children and young adults with B-cell acute lymphoblastic leukemia that had not responded to standard treatments or had relapsed at least twice. The approval was based on results from a phase II clinical trial, showing that more than 80 percent of the children and young adults who were treated with tisagenlecleucel achieved a remission within three months of receiving the CAR T-cell therapy (453). This revolutionary immunotherapeutic has allowed some children with leukemia, like **Cayden Addison**, p. 114, to experience complete remission following treatment. In a recent study, long-term follow-up of patients treated with tisagenlecleucel showed that more than 60 percent were living three years or longer after their first infusion of CAR T cells, suggesting that CAR T cells can lead to durable cancer control (454).

continued on page 116

In 2022, 264 clinical trials were initiated, **globally**, investigating the use of CAR T-cell therapy in cancer treatment. **The number of trials evaluating CAR T-cell therapy in solid tumors increased by 30 percent** compared to 2021 (332).



"By focusing on these new treatments, research can provide the best that the future has to offer... I am hopeful."

– Emily Graton

ISABELLA (BELLA) SNOW FRASER
Age 12 • West Newbury, VT

Reclaiming Childhood, Thanks to Immunotherapy

A Message from Emily Graton, Isabella's Mother

Bella was diagnosed with alveolar soft part sarcoma (ASPS) in 2016. She was 6, just starting kindergarten. Bella had surgery to remove the tumor from her arm. Her doctors thought they were able to get it all out and that the tumor was not likely to return. However, a follow-up scan showed that the cancer had spread to her lungs. After more surgeries to remove the nodes from her lungs, Bella received chemotherapy for about a year, but her cancer kept growing. One of Bella's providers informed us about a clinical trial that was evaluating atezolizumab (Tecentriq) for ASPS and we jumped on that opportunity. Since starting on the trial drug, the cancer has stopped growing and there have been few to no side effects. She seems healthier than ever. It is like Bella is back to normal.

The first sign of Bella's illness appeared when she was 6 years old. She was reaching over the bathtub and got a bump on her arm. Initially, the doctors thought it was a deep bruise that might take months to heal. Months went by but the bump never went away. At that point, the doctors suspected nerve damage, which led to an ultrasound. After the ultrasound did not show anything, she was taken for a biopsy. The mass was taken out of her arm, and the biopsy led to her diagnosis of ASPS. My mother had been diagnosed with stage IV lung cancer earlier that year. And now my daughter was faced with one of the rarest cancers in the world. It was a very scary situation for our family. But I was determined to find everything there was to know about the disease and work toward a solution.

After Bella's surgery, we went back for routine scans to ensure that the cancer was no longer growing. About five years passed without incident. I became involved with some online forums of fellow patients with ASPS, and someone suggested Bella should have more follow-up. At our request, the doctors ordered additional tests. And as it happened, her chest scan showed that the cancer had spread to her lungs.

Bella had more surgeries to have three of the lung nodes removed. She then started on a clinical trial that was testing an oral chemotherapy. She stayed on the study for a year, but the treatment was not working. The masses continued to grow, and she had some serious side effects. This was also during the pandemic. I missed a lot of work and Bella missed a lot of school just trying to fight this off. Fortunately, one of Bella's providers called me about a promising clinical trial for patients with ASPS that was testing the immunotherapy atezolizumab. We were on standby for a while because of Bella's age. But once the trial gave us the go-ahead, we couldn't wait to get started.

Bella's initial treatments on the trial were at the National Cancer Institute, so we had to travel for several weeks at a time. Bella missed a lot of school and I had to change jobs. Then she began receiving treatments at the Dana-Farber Cancer Institute in Boston. It's still a four-hour trip each way. Every three weeks, we get up at 3 a.m, drive to the bus, take it to Boston and then make our way to Dana-Farber. It's a challenge, but I would travel across the world for Bella, for a chance to beat this cancer.

Atezolizumab has been remarkable in many ways. First, the cancer has stopped growing. We haven't seen any growth in over a year, but we are really hoping to see some shrinkage in her cancer. As soon as we see that, we're going to have a celebration.

Also, there are minimal side effects. Bella gets an IV infusion for 30 minutes, which is a lot shorter than her prior treatments. She is happy, her hair is growing back, she wants to eat, and is active. I'm very thankful for this drug and what it has done for Bella. Her biggest side effect is fatigue. She needs more sleep. So, we schedule everything around Bella, to make sure that she's doing okay. It is amazing to see how positive she stays throughout it all. She is a champion.

I cannot overstate the importance of funding cancer research. Without clinical trials such as the one in which Bella is participating, and without the funding to make this research happen, Bella would not be able to run around like she does today. She would not be able to enjoy these times with her family and friends. Because of cancer research, she gets to live a normal life; she gets to smile more. Without these treatments, it would just end.

Patients, families, and their communities rely on these treatments. Kids like Bella are our future. Without them, we are not going to go forward. By focusing on these new treatments, research can provide the best that the future has to offer. Healing those who need it the most will lead to a better world. I am hopeful. Looking toward hope can be exhausting sometimes, but it's all worth it in the end.

Scan the QR code
to watch Isabella's video interview.

"...I have made it my mission to use my voice to advocate for and bring attention to the cause."

ALEXIS BROWNING
Age 28 • Lexington, KY

Navigating Young Adulthood with a Cancer Diagnosis

In 2019, I noticed that my right leg was bigger than my left leg. Initially, I did not give much thought to it because it is my dominant leg and it just looked like a big thigh muscle. Eventually it became painful, prompting me to see a physician. I had an MRI, which showed that I had an 18-centimeter tumor wrapped around my right femur bone. Follow-up scans and biopsies revealed that the cancer had metastasized to my lungs, which led to my diagnosis of stage IV alveolar soft part sarcoma (ASPS). It was truly horrifying. I could not wrap my mind around what was happening. I did some research on the cancer and realized how rare the disease is and the devastatingly low survival rates.

Immediately after my diagnosis, I traveled to the Dana-Farber Cancer Institute in Boston to meet with a sarcoma specialist. It was an excruciating trip because it reminded me how severe my situation was. My oncologist told me that I had between 10 and 20 years left. He suggested a clinical trial at NIH that was evaluating an immune checkpoint inhibitor, atezolizumab, for ASPS. Before enrolling in the trial, I decided to freeze my eggs because it was always my dream to have a family and be a mother someday. I took the time to do that as quickly as possible.

After signing off on several really intimidating consent forms, and undergoing more scans and biopsies, I eventually joined the clinical trial. I stayed on the treatment for two and a half years. My cancer remained stable the entire time. However, I was living with consistent pain and decided to leave the trial to have my primary tumor surgically resected. The goal was to alleviate the pain and improve my quality of life. We did not have much hope for success because of the way the tumor wrapped around the bone. But when I woke up after my procedure, my surgeon told me that miraculously, he did achieve clear margins. There was no cancer in my leg any longer. The pain completely subsided. I had a restored quality of life.

Right after the surgery I went back on the same treatment, atezolizumab. However, I was no longer traveling to NIH but making day trips to the Ohio State University Cancer Center with my parents for my treatment. Thankfully, in December 2022, atezolizumab was approved by FDA for the treatment of ASPS. This meant that I could get treated locally in Louisville. Currently, I travel 15 minutes down the street to get my infusion. That is another massive victory that I have had the luxury of experiencing during my time battling ASPS. I feel fortunate to have been a witness to actual scientific progress and to be treated with the only approved option for ASPS.

I will continue to receive treatment every 21 days. My disease has remained stable even though I am still living with the remaining cancer in my lungs. While I remind myself that I get to live a mostly normal life and I am fortunate not to have disease progression or harsh side effects, it is hard sometimes. I feel like a financial and emotional burden to my family and the people that are closest to me. I have also learned that I will not be able to stop treatment long enough to carry out my own pregnancy. I have always dreamed of being a mother and this is weighing most on my soul right now.

I am fortunate to have an amazing village of supporters who love me, and I can feel that deep in my core. On days when I just do not have any grace to give, they help me find little moments of comfort and joy in the mundane and in the darkness. And I know that I could not do it without them. These are things that cannot be discounted.

During my time living with ASPS, I have made it my mission to use my voice to advocate for and bring attention to the cause. It gives me a purpose and shows me that I am not alone.

Scan the QR code
to watch Alexis' video interview.

"...Funding for cancer research is vital. Immunotherapy and CAR T-cell therapy would not have been options without research."

– Courtney Addison

CAYDEN ADDISON
Age 6 • Chesapeake, VA

Playing and Enjoying Childhood, Thanks to CAR T-cell Therapy

A Message from Courtney Addison, Cayden's Mother

Cayden was only 3 years old when he was diagnosed with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), in April 2020. Before his diagnosis, Cayden was full of energy, and he loved to eat. But then he started to complain about leg pain. We first thought it was just a growth spurt, but the pain got so bad that he could not walk. He also lost his appetite. That wasn't like him at all, and I knew something was not right. It was the height of COVID-19, but I took him to the emergency room. All of his tests came back negative. I then talked to his pediatrician and after many blood tests, Cayden was diagnosed with leukemia. I just remember collapsing in my husband's arms. My hands and feet went numb. My heart was pounding, and I sobbed. Cayden was always a very healthy child, and to go from a healthy, playful young boy to a leukemia diagnosis was devastating. I just remember being so shocked and overwhelmed, but we did not have the time to process the news because everything moved incredibly fast right after his diagnosis.

Cayden's initial treatment was chemotherapy, and it started within hours of his diagnosis. Cayden experienced side effects from his treatment. He was constantly nauseous. His appetite changed. He would get moody from the steroids that he had to take. And in March 2021, he developed sepsis and a fungal lung infection and was hospitalized for over a month. After two years of receiving chemotherapy every day, we celebrated the end of his treatment in April 2022. Then in February 2023, his cancer relapsed. Initially, he received chemotherapy drugs that were similar to his first treatments. He then received a new type of immunotherapy drug, called blinatumomab (Blincyto). He had to wear a bag for 30 days so that he could constantly receive medication. Because Cayden's leukemia is rare and affects only 3% of patients with leukemia, and has a high risk of relapse, his doctors suggested the possibility of CAR T-cell therapy.

We went to Duke University in North Carolina for CAR T-cell therapy. His doctors collected as many white cells as they could and shipped them off to the company that genetically engineered those cells to create the CAR T cells. Leading up to the treatment, Cayden had about three days of chemotherapy to prepare his body for the infusion. On the day of his treatment, three nurses infused CAR T cells into his body and that was it. He did not need to continue chemotherapy anymore. There are some preventative medications he has to take to protect his lungs and body from infection. But besides that, it was almost like a one-and-done type of thing and just monitoring afterward.

Cayden has been handling everything phenomenally since the treatment. He experienced a couple of days of nausea, but besides that, he's been his normal playful little kid self, running around the house and eating well at home and outside. Immunotherapy is amazing. I wish he could have received this treatment the first go-around. With the regular chemotherapy, there were still some leukemia cells in his body. After immunotherapy, he has been in complete remission. He barely has any side effects at all. He is completely normal compared to when he received the standard treatment.

I say to members of Congress that funding for cancer research is vital. Immunotherapy and CAR T-cell therapy would not have been options without research. It is important that we continue to fund research so that our children do not have to go through this. We must find a cure and until that day comes, we need to find better treatment alternatives that have less harsh side effects. This experience has sparked a fire in me, and has forever changed my life. Our kids deserve better. I do not want any other family to go through what my family has gone through. Cayden has his whole life ahead of him. I don't want him to have to deal with years of side effects. I don't want this to be his whole childhood memory. I want him to have a life where he can do whatever he dreams for the rest of his life. Funding is critical so that we can continue to make advancements against cancer, including treatment options with less side effects so that Cayden and other kids affected by cancer do not have to deal with consequences of cancer treatment for rest of their lives.

Scan the QR code
to watch Cayden's video interview.

SPOTLIGHT

SIDEBAR 39

T Cell-based Adoptive Cell Therapy

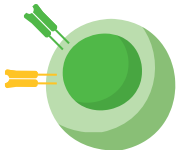
Adoptive T cell therapy, also called cellular immunotherapy, dramatically increases the number of cancer-killing immune T cells, thus boosting a patient's immune system to seek and destroy cancer cells. It is a complex and multistep medical procedure. During the treatment, T cells are harvested from the patient to expand them in number and/or genetically modify them in the laboratory to enhance their cancer-fighting capabilities. The expanded and/or genetically enhanced T cells are then reinfused in the patient to help eliminate cancer cells.

TYPES OF ADOPTIVE T-CELL THERAPY

There are three main types of adoptive T-cell therapy. As of July 31, 2023, only one type, chimeric antigen receptor (CAR) T-cell therapy, has been approved by the U.S. Food and Drug Administration.

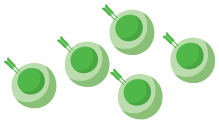
Chimeric antigen receptor (CAR) T-cell therapy

T cells are harvested from a patient's blood and genetically modified in the laboratory so that they have a synthetic protein called a CAR on their surface that recognizes and binds to a specific protein on the surface of the patient's cancer cells. The genetically modified T cells are expanded in number and infused back into the patient. The CAR modification helps the T cells directly bind to and eradicate the patient's cancer cells.



T-cell receptor (TCR) T-cell therapy

T cells are harvested from a patient's blood and genetically modified in the laboratory so that they have a synthetic protein called TCR on their surface, which recognizes certain protein fragments on the surface of the patient's cancer cells. The genetically modified T cells are expanded in number and infused back into the patient. The TCR modification helps the T cells seek out the patient's cancer cells more effectively and triggers them to attack the patient's cancer cells.



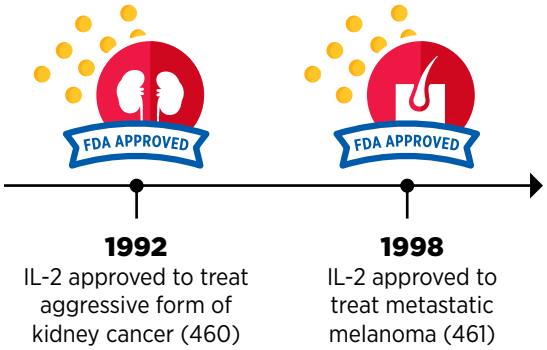
Tumor-infiltrating lymphocyte (TIL) therapy

T cells are harvested directly from a patient's tumor, expanded in number in the laboratory, and infused back into the patient. Many of these T cells naturally recognize and kill the patient's cancer cells.

Since 2017, five additional CAR T-cell therapies have been approved by FDA, all for the treatment of blood cancers, including NHL, leukemia, and most recently, multiple myeloma (see **Sidebar 40**, p. 117). Collectively, these treatments have transformed the lives of adult and pediatric patients with blood cancers (455). As one example, based on a recent analysis, axicabtagene ciloleucel (Yescarta), which was also approved by FDA in 2017, is the first treatment in nearly three decades to improve overall survival in relapsed or refractory large B-cell lymphoma (456).

Generating CAR T cells is a complex procedure that can only be performed at specially certified health care facilities by highly trained medical professionals. Additionally, like other cancer treatments, CAR T-cell therapies can cause side effects, some of which can be potentially life-threatening. Another issue that researchers are trying to address is the fact that CAR T-cell therapies have so far proven less successful against solid tumors. Developing simpler and safer ways to bring the promise of this class of immunotherapeutics to more patients with different cancer types is an area of active research (see **On the Horizon for Immunotherapy**, p. 128).

INTERLEUKIN-2 (IL-2)



SIDEBAR 40

CAR T-cell Therapies Approved by the U.S. Food and Drug Administration

As of July 31, 2023, there are six distinct FDA-approved CAR T-cell therapies to treat different cancer types:

APPROVAL YEAR	THERAPY NAME	TREATMENT FOR
2022	Ciltacabtagene autoleucel (Carvykti)	Adult patients with relapsed or refractory multiple myeloma
2021	Idecabtagene vicleucel (Abecma)	Adult patients with relapsed or refractory multiple myeloma
2021	Lisocabtagene maraleucel (Breyanzi)	Adult patients with certain types of B-cell lymphoma
2020	Brexucabtagene autoleucel* (Tecartus)	Patients with relapsed or refractory mantle cell lymphoma
2017	Tisagenlecleucel* (Kymriah)	Adult patients with certain types of B-cell lymphoma and young adult patients up to age 25 with certain types of lymphoblastic leukemia
2017	Axicabtagene ciloleucel* (Yescarta)	Adult patients with certain types of B-cell lymphoma

*These therapeutics have received expanded approvals for the treatment of additional blood cancer types since their first approvals by FDA.

Enhancing Immune Cell Function

Immune cells communicate with each other and with their surrounding cells by direct contact as well as through the release of a class of molecules called cytokines. Cytokines are also produced by nonimmune cells and play an essential role in rapidly activating the immune system in response to cellular stresses, such as infection, inflammation, and cancer (457).

For many decades, researchers have been investigating the natural cancer killing ability of two cytokines, interferon-alpha (IFNα) and interleukin-2 (IL-2), to boost the cancer-killing function of the immune system (458). Discoveries in the late 1960s established the role of interferons in suppressing tumor growth, which led to subsequent clinical trials confirming their anticancer effects (449). In 1986, IFNα became the first FDA-approved cancer immunotherapy when it was approved for the treatment of a rare blood cancer known as hairy-cell leukemia (459).

Although cytokines have shown some promise as immunotherapeutics, their success has been limited. One limitation is that cytokines do not persist very long in the body, so ongoing research is developing more stable versions of cytokines (461). Another challenge is the significant adverse effects when cytokines are administered as a systemic treatment. Researchers are exploring ways to enhance the efficacy of interferons while minimizing their side effects, for example, by delivering them in or near tumors (461).

The FDA approval of nadofaragene firadenovec-vncg (Adstiladrin) in December 2022, was a major advance in the field of interferon-based cancer immunotherapy. The FDA approved nadofaragene firadenovec-vncg for the treatment of adult patients with high-risk, non–muscle-invasive bladder cancer (NMIBC) that did not respond to Bacillus Calmette-Guérin (BCG) treatment.

More than 82,000 new cases of bladder cancer will be diagnosed in the United States in 2023 (28). Non–muscle-invasive bladder cancer—a type of cancer that has grown through the lining of the bladder but hasn't yet invaded the muscle layer—makes up around 75 percent of all new cases of bladder cancer (462). Patients with high-risk NMIBC are usually treated with BCG—an immunotherapeutic that was originally developed as a vaccine against tuberculosis (TB)—which is instilled directly into the bladder. While 80 percent of patients initially respond to BCG, within a year over half of patients with an initial response experience recurrence and progression of cancer, and many develop disease that becomes BCG-unresponsive (463,464).

continued on page 120

"We have lots of needs in this country, but saving people's lives is what's most important and we need to fund that."

LESA KIRKMAN
Age 61 • Niceville, FL

Reclaiming Health After Gene Therapy for Bladder Cancer

I have no family history of cancer. I never smoked; I lived a healthy lifestyle. So, in July 2016, when I was diagnosed with stage T1 high grade bladder cancer, it was a complete shock. After two surgeries in July and August 2016 to remove the tumors (both carcinoma in situ and Ta high grade bladder cancers), I was put on Bacillus Calmette-Guerin (BCG) therapy, a gold standard treatment for this disease. I received BCG for two years, with an additional surgery in December 2016 to remove tumors. When, in April 2018, tumors recurred, I was considered non-responsive to BCG and could not continue with the treatment plan. My oncologist talked to me about a clinical trial that was testing a novel gene therapy, nadofaragene firadenovec-vncg (Adstiladrin) for bladder cancer. I decided to participate because I believed that it was the best course of action for me. I first received the gene therapy in 2018 and have had no recurrences in the past five years. I ended treatment in 2021 and am just living my life.

In April 2016, I went to see my gynecologist after I noticed blood in my urine. They treated me for a urinary tract infection for about six weeks, but that did not resolve the problem. A follow-up evaluation with a urologist led to a CT scan of my abdomen and bladder, which found the tumors. I had never heard of bladder cancer and was scared. There was no history of cancer in my family. I was active and led a healthy life. So, this was a huge shock.

Immediately after my diagnosis, I had my first surgery. Later, in August, I underwent a second surgery to have additional tumors removed. About six weeks later I started on BCG treatment, which is considered the gold standard for bladder cancer treatment. I received an initial induction of six treatments over six weeks followed by a brief break. I went back for BCG treatments about every three months until the beginning of 2018. Over this period, I also had additional surgeries to have more tumors removed. Following my surgery in April 2018, my physician determined that I was no longer responding to BCG.

As we were evaluating the next course of action, my oncologist at the MD Anderson Cancer Center informed me that I would be an ideal candidate for a clinical trial that was evaluating a new gene therapy. I decided to participate and started on the trial in May 2018. For the next three years, I went back to MD Anderson every three months. The first visit was to have a cystoscopy, which looks at the bladder internally with a camera, to ensure there were no new tumors. Two weeks later, I went back to MD Anderson for the instillation of the medication, nadofaragene firadenovec-vncg. Since I started on this gene therapy in 2018, I have had no evidence of disease. In May 2021, we were able to discontinue the treatment. Currently, I'm just monitored periodically through CT scans, lung scans, and EKGs to ensure that no tumors have come back.

Fortunately, I didn't have a lot of side effects from the treatments. I did experience some fatigue as well as muscle and joint pain, which all cleared up since stopping the treatments. Personally, I'm doing great. I play tennis. I walk with my daughter three to four times a week. I travel. In fact, we just got back from a monthlong trip to Europe. I am just living my life.

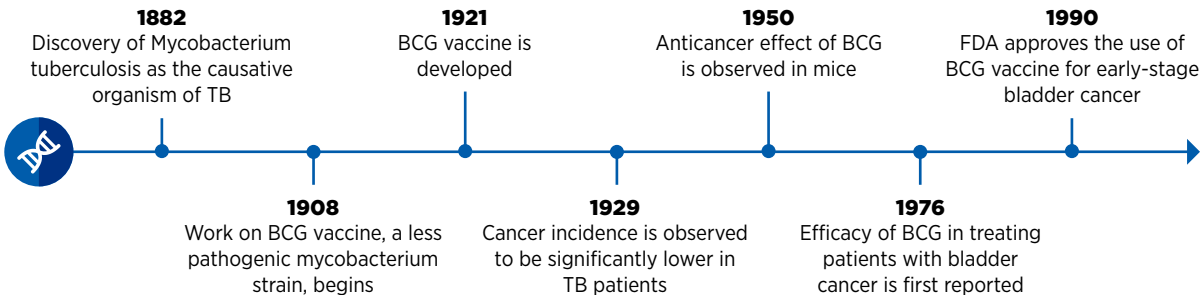
Making progress in medicine—finding the causes and cure for cancers—is of national importance. I don't know anyone who has not been touched by cancer or whose family has not been affected by cancer. Therefore, the importance of funding cancer research or any type of medical research cannot be understated. We have lots of needs in this country, but saving people's lives is what's most important and we need to fund that. No matter your political affiliation, everyone must recognize that at some point their lives will be touched by cancer. That's why this research is vital.

I'm thankful to those people who participated in the earlier phases of the clinical research, when the safety and efficacy of the drug weren't known. I had an incredible experience participating in the trial. Giving other patients the opportunity to have a different course of medicine, a different course in life, is worth it. It takes many people to make advancements in medicine, and I believe we all must do our part.

Scan the QR code
to watch Lesa's video interview.

SPOTLIGHT

BCG IMMUNOTHERAPY AGAINST CANCER



Currently BCG immunotherapy remains a standard of care for high-risk non–muscle-invasive bladder cancer.

BCG, Bacillus Calmette–Guérin. Developed from (465).

Patients who do not respond to BCG have very few treatment options other than surgical removal of the bladder. Although potentially curative, such surgical therapy is associated with high rates of complication. Additionally, many patients with underlying health conditions are unwilling or unable to undergo the surgery (464). Therefore, alternative treatments for patients with bladder cancer, such as **Lesa Kirkman**, p. 118, are an urgent medical need, and are addressed by the nadofaragene firadenovec-vncg approval.

Nadofaragene firadenovec-vncg is a novel therapeutic. It is the first gene therapy approved for bladder cancer. When instilled into the bladder through a urinary catheter, the therapeutic infiltrates the bladder cells and delivers a gene encoding interferon alpha 2b (IFNα2b) into the DNA of the cells it infiltrates. Once the gene is incorporated into the bladder cells, they produce the IFNα2b protein, which blocks bladder cancer growth through the activation of immune cells, among other mechanisms (466). The approval was based on a Phase II, single arm study with registration intent. Findings of the study showed that among 51 percent of patients treated with nadofaragene firadenovec-vncg no cancer cells could be detected in their urine and in the urinary bladder tissue (464).

Researchers are also evaluating IFNα2b treatment as a potential therapy for other cancer types. As one example, recent data show that people with low-grade lymphomatoid granulomatosis, a rare condition that can progress into an aggressive B-cell lymphoma, can live for decades after diagnosis when treated with IFNα2b (467). This is a remarkable advance compared to findings from past studies showing median survival of less than two years for people with lymphomatoid granulomatosis.

Directing the Immune System to Cancer Cells

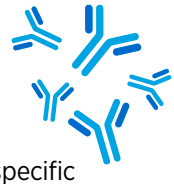
An immune cell must find a cancer cell before it can attack and eliminate it. Many therapeutic antibodies approved by FDA for the treatment of various types of cancer work, at least in part, by helping immune cells find cancer cells. Because of the effectiveness and promise of antibody-based immunotherapeutics, many researchers have been working to develop new as well as improved versions of this important class of anticancer therapeutics.

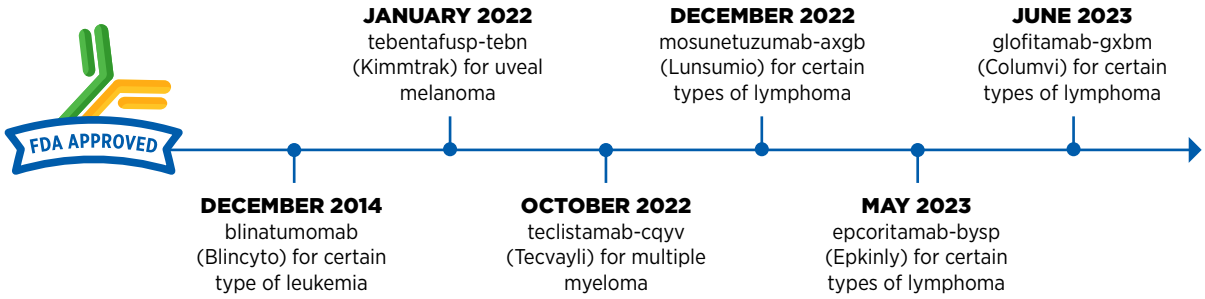
One class of recently developed therapeutic antibodies is known as T-cell engaging bispecific antibodies. Using two or more arms that are engineered into these antibody particles, these immunotherapeutics bind to immune cells and cancer cells simultaneously. By acting as a connector, T-cell engaging bispecific antibodies bring cancer cells into close proximity with T cells, which are then activated and eliminate the cancer cells.

The first of these agents, blinatumomab (Blincyto), was approved by FDA in December 2014 for treating certain patients with a type of acute lymphoblastic leukemia (ALL) called B-cell ALL (468). Unprecedented advances in genetic engineering, molecular biology, and immunology over the past decade have led to a rapid proliferation in this innovative new area of cancer medicine. Between August 1, 2022, and July 31, 2023, FDA approved four new T-cell engaging bispecific antibodies for the treatment of a number of hematologic cancers.

In October 2022, FDA approved teclistamab-cqyv (Tecvayli) for adult patients with multiple myeloma that has relapsed after, or never responded to, at least four prior lines of therapy. Teclistamab-cqyv attaches to a molecule called CD3 on T cells with one arm and to B-cell maturation antigen (BCMA),

Therapeutic antibodies are proteins that are **effective in the treatment of numerous cancer types** and function in several different ways by attaching to a specific molecule in the body.





As of July 31, 2023, **FDA has approved six T-cell engaging bispecific antibodies for the treatment of cancer** (469).

a molecule that is abundant on the surface of most multiple myeloma cells, with the second arm. By attaching to these molecules on different cells, teclistamab-cqyv brings the two cell types together, directing the T cells to home in on the myeloma cells. As a result, T cells are activated and they destroy the adjacent myeloma cells.

The FDA approval of teclistamab-cqyv was based on data from a phase I/II clinical trial that evaluated the immunotherapeutic in 110 patients who had stopped responding to at least three classes of drugs prior to receiving teclistamab-cqyv (470). More than 60 percent of participants responded to therapy with teclistamab-cqyv (470). Historically, patients with multiple myeloma that has progressed following multiple classes of treatment have been extremely challenging to treat. In fact, with immunotherapeutics such as daratumumab, which is approved for these patients, response is seen only in 30 percent of patients or fewer (471). Therefore, the approval of teclistamab-cqyv brings hope to patients like **Cindy Brown**, p. 122, by providing them with a new and effective treatment option.

It is important to note that some of these immunotherapeutics can have life-threatening side effects if not managed immediately and appropriately by trained medical professionals. For example, FDA approval of teclistamab-cqyv comes with a warning of life-threatening adverse events, such as cytokine release syndrome and neurologic toxicity, which are usually manageable. Because of these risks, teclistamab-cqyv is available only through a restricted program, called the Tecvayli Risk Evaluation and Mitigation Strategy (REMS).

The three other T-cell engaging bispecific antibodies approved by FDA during the 12 months covered in this report—mosunetuzumab-axgb (Lunsumio), epcoritamab-bysp (Epkinly), and glofitamab-gxbm (Columvi)—all work by attaching to CD3 on T cells and to CD20, a protein that is found in abundance on the surface of cancerous B cells. By bringing the two cell types together, these therapeutics help activate the T cells to destroy cancerous B cells.

Mosunetuzumab-axgb was approved by FDA in December 2022 for the treatment of certain patients with relapsed or refractory follicular lymphoma, the second most common form of NHL diagnosed in the United States. Follicular lymphoma is a slow-growing cancer that arises in immune cells called B cells (see **Sidebar 38**, p. 100) but can eventually progress to become a fatal disease. Most B cells, including follicular lymphoma B cells, have a protein called CD20 on their surface, making CD20-targeted therapeutic antibodies an attractive treatment option for this cancer.

CD20-targeting therapeutic antibodies have been approved previously by FDA for the treatment of follicular lymphoma and have a very high response rate. Rituximab (approved in 2006) and obinutuzumab (approved in 2016) are two examples. However, it should be noted that these antibodies work differently from mosunetuzumab-axgb. Mosunetuzumab-axgb is the first T-cell engaging bispecific antibody approved for follicular lymphoma.

The FDA approval of mosunetuzumab-axgb was based on results from a phase I/II clinical trial in which the therapeutic was given to 90 patients with follicular lymphoma that had relapsed or stopped responding to other treatments. All patients had received at least two prior treatments, including a CD20-targeting therapeutic antibody. The results from the trial showed that 80 percent of patients whose disease was not responding to prior treatments had partial or complete tumor shrinkage, with 60 percent exhibiting complete shrinkage following treatment with mosunetuzumab-axgb (472). The complete response rate was significantly higher than that observed with current standard treatments. The approval of mosunetuzumab-axgb comes with a warning for cytokine release syndrome, which may occur as a result of the hyperactivation of T cells that are targeting the lymphoma.

Both epcoritamab-bysp and glofitamab-gxbm were approved for the treatment of patients with certain types of NHL. Diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma are types of NHL that arise from B cells. DLBCL is the most common form of the disease, accounting for 30 to 40

continued on page 124

"I am also a huge advocate of clinical trials. There is no way to advance science without people being willing to participate in research studies."

CINDY BROWN
Age 58 • Coto De Caza, CA

Spending Quality Time with Family, Thanks to Immunotherapy

Nine years ago, I was experiencing excruciating pain in my right hip. After physicians prescribed injections that helped only briefly, I got an MRI that detected a tumor in my sacrum. Follow-up tests led to my diagnosis of multiple myeloma–a type of blood cancer. I was 48 at the time, had recently been remarried, and had school-age children still at home. I was devastated. After 14 different chemotherapies and two stem cell transplants, I decided to enroll in a phase I clinical trial evaluating the immunotherapeutic teclistamab-cqyv (Tecvayli). This drug has been a game changer. I have been in what is called a complete response for over three years and living a normal life, which is incredible.

It all started in April 2014. I had hip and leg pain for several months . It was so severe that I could not lie down to sleep. I saw multiple physicians who assumed that it was something in my spine, like a pinched nerve or a herniated disc. I received a few injections that provided short-term relief, but the pain kept getting worse. Eventually I got an MRI, which showed a tumor in my sacrum, almost the size of a grapefruit. Biopsies and other diagnostic tests confirmed that I had multiple myeloma.

I was in a state of shock. I was only 48, otherwise very healthy. In fact, I just had my routine lab work done a couple of months before and everything looked good. This just did not make sense. I had never heard of multiple myeloma. I was devastated.

I immediately sought treatment from an oncologist who put me on the standard treatment path for this disease. I started on a combination of steroids and chemotherapy. Additionally, I received radiation therapy to my sacrum to relieve the pain. Once that oncologist believed I was ready, I was sent to a multiple myeloma specialist to start the stem cell transplant process. Unfortunately, during that transition time, I had almost a full relapse and needed three more rounds of inpatient chemotherapy with an intense seven-drug regimen.

I received two types of stem cell transplants: first, an autologous transplant, where I received my own stem cells that had been collected prior to chemotherapy; this was followed 9 weeks later by an allogenic transplant, where I received donor stem cells from one of my brothers. The recovery after the transplants was rough, especially after the allogenic transplant. I went into severe heart failure. Fortunately, the doctors were able to manage and correct the condition. It was a rough couple of weeks for me and my family with lots of prayers.

I have had a couple of relapses since my allogenic transplant. Some of the treatments that the doctors tried only worked for brief periods of time. I experienced a broken jaw and more radiation. Iearly 2019, I developed a tumor in my arm. The tumor did not respond to chemo so in October I had surgery to place a rod between my elbow and shoulder, followed by radiation. I knew that something had to change with my next treatment. Unfortunately, I was running out of options. That is when my myeloma specialist at the City of Hope Cancer Center told me about the phase I clinical trial evaluating teclistamab-cqyv (Tecvayli). She was excited about the study and felt it would be a great option for me, which gave me a tremendous amount of hope.

I started treatment in March 2020. For the first 11 days, I was in the hospital, where I received step-up dosing to make sure I could tolerate the drug. Then I moved to an outpatient setting. This new treatment has really been different from any of my other treatments. Most importantly, this is the longest remission I have had. I am almost at the three-and-a-half-year mark, and I have never gone even close to this long on any other course of treatment. Also, compared to other treatments, the side effects have not been significant. I do get respiratory infections sometimes, but I take medications to manage that.

Thanks to this new immunotherapy, today I'm doing great.

I'm extremely grateful to the researchers who developed this immunotherapy. Thanks to the treatment, I am living a normal life. I do Pilates, go out with friends, spend time with family, travel, and pursue my hobbies. It has been nice to have a treatment that does not leave me feeling tired or bedridden.

I am also a huge advocate of clinical trials. There is no way to advance science without people being willing to participate in research studies. It is important for Congress to understand that I am here today because of a clinical trial that changed the trajectory of my disease. It is critically important that cancer research continues to be funded because of people like me; I would not be here today without this groundbreaking research. The more research that can be done, the more time people will get to spend with their families, watch their children grow up, and be productive members of society.

Scan the QR code
to watch Cindy's video interview.

percent of all cases (473). DLBCL often develops from evolution of other types of lymphoma, including follicular lymphoma, that have been undergoing therapy. Different subtypes of DLBCL exist. When a patient does not fit into any of those subtypes, it is classified as DLBCL not otherwise specified.

Epcoritamab-bysp was approved by FDA in May 2023 for patients with either DLBCL not otherwise specified or high-grade B-cell lymphoma whose disease did not respond to or relapsed following two or more lines of systemic therapy. The approval was based on results from a phase I/II clinical trial which showed that 61 percent of patients responded to the therapeutic and 38 percent of patients achieved complete responses with no signs or symptoms of cancer following the treatment. The approval of epcoritamab-bysp includes a warning that the treatment can cause serious or life-threatening immune-related adverse reactions and should only be administered by qualified health care professionals with appropriate medical support.

Glofitamab-gxbm was approved in June 2023 for patients with DLBCL, not otherwise specified or large B-cell lymphoma arising from follicular lymphoma, who relapsed after or did not respond to two or more lines of systemic therapy. The approval was based on data from a phase I/II study in which more than half of all patients responded to the treatment, with approximately 40 percent achieving complete responses, meaning researchers could not detect signs or symptoms of cancer (474).

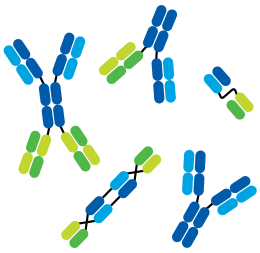
Glofitamab-gxbm has a few unique characteristics that set it apart from the other T-cell engaging bispecific antibodies discussed in this section. First, glofitamab-gxbm is approved to be administered for a fixed duration of about 8.5 months, whereas most other agents are administered until the disease progresses or the therapeutic cannot be tolerated any longer. The fixed-duration approach is used because data indicate that administration until disease progression is not required to achieve a durable remission with glofitamab. The fixed-duration approach is attractive to patients because it provides them with a shorter and potentially less toxic treatment option. Second, glofitamab-gxbm has two arms to latch onto CD20 unlike epcoritamab-bysp and mosunetuzumab-axgb, which only have one, and is therefore expected to be more potent. The approval of glofitamab-gxbm includes a warning that the treatment can cause serious or life-threatening immune-related adverse reactions and should only be administered by qualified health care professionals with appropriate medical support.

While ongoing research is needed to identify ways to minimize the adverse effects, T-cell engaging bispecific antibodies are now offering a wide selection of new therapeutics and providing hope to many patients with advanced cancer who are often out of options and urgently need effective treatments for their rapidly progressing disease.

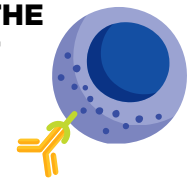
Another group of therapeutic antibodies that mark cancer cells for elimination by the immune system uses a natural process called antibody-dependent cellular cytotoxicity. When the immune system detects a pathogen or damaged cells, B cells produce antibodies that flag unwanted cells or organisms, which are then recognized and killed by immune cells such as NK cells (see **Sidebar 38**, p. 100) (475). Researchers are using this knowledge to develop antibodies that bind to specific targets on cancer cells and invoke antibody-dependent cellular cytotoxicity to kill them.

Many therapeutic antibodies that work this way have been approved by FDA and are benefiting numerous patients with different cancer types including solid tumors, hematologic cancers, and pediatric cancers. As one example, dinutuximab (Unituxin), which was approved in 2015 for treating children with high-risk neuroblastoma, works by attaching to a protein, GD2, on neuroblastoma cells and flagging them for destruction by immune

More than 130 bispecific antibodies are currently being evaluated globally as anticancer therapeutics. Sixty seven percent of these are being tested **in solid tumors**, 24 percent **in blood cancers**, and 9 percent in both (332).



IMMUNOTHERAPEUTICS APPROVED BY FDA IN THE PAST FIVE YEARS THAT INVOKE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY



2018 **mogamulizumab-kpkc**
Targets CCR4 to treat certain type of leukemia

2020 **isatuximab-irfc**
Targets CD38 to treat multiple myeloma

tafasitamab-cxix
Targets CD19 to treat certain type of lymphoma

margetuximab-cmkb
Targets HER-2 to treat certain type of breast cancer

naxitamab-gqgk
Targets GD2 to treat neuroblastoma

cells. Decades of basic, translational, and clinical research, starting from the recognition of GD2 as a tumor protein in 1984, led to the development of dinutuximab. Recent data demonstrate that the therapeutic antibody is extending lives for many children with high-risk neuroblastoma (476). Since the approval of dinutuximab in 2015, the FDA has approved a second therapeutic, naxitamab-gqgk (Danyelza), that works similarly to dinutuximab, for the treatment of patients with neuroblastoma.

Current Challenges in Cancer Immunotherapy

As described throughout this section, over the past decade, immunotherapeutics have revolutionized the landscape of cancer treatment. However, immunotherapeutics have been successful in treating only a fraction of patients with cancer with several challenges remaining. These include serious and even life-threatening adverse effects; patients who respond initially but develop resistance over time; and the current gaps in our understanding of how to integrate immunotherapies with standard cancer therapies. In this section we outline some of the current limitations and known challenges of cancer immunotherapy.

Knowledge Gaps in Predicting Response to Immunotherapy

Immunotherapeutics have shown extremely durable responses in certain patients with cancer. To determine if a patient may respond to these therapeutics, clinicians use biomarkers, molecules that can identify certain characteristics of a cell or a tissue. The most common biomarkers currently used to select patients for ICI treatment are the presence of certain surface proteins on cancer cells and the presence of specific molecular characteristics.

The presence of a biomarker, for example surface levels of PD-L1 protein, informs the clinician whether a patient might respond to a PD-1/PD-L1 targeted immunotherapy, such as pembrolizumab. However, one concern is that levels of these biomarkers are not always consistent with one study finding that levels of PD-L1 change over time and are not the most reliable biomarker for anti-PD-1 therapies (477).

Another major challenge in cancer immunology biomarker research is the lack of diversity in genetic databases and underrepresentation of individuals of non-European genetic ancestry (478). As a result, gaps remain in our understanding of the ancestry-related differences of tumors and the immune system, which are key contributing factors in determining efficacy of cancer immunotherapies. As one example, one study found that Black individuals can be misclassified as having a cancer with a high tumor mutational burden (TMB-h), a biomarker used in some cases to select patients for treatment with certain immunotherapeutics, including pembrolizumab. Further, the study found that patients of African ancestry classified as h-TMB did not respond to pembrolizumab because of this misclassification (479). These findings illustrate the importance of increasing diversity of genetic databases to include more individuals from non-European ancestries.

Like other anticancer therapeutics, one concern after ICI treatment is the possibility of cancer recurrence. Recurrence or relapse of metastatic disease after initial response may occur because of acquired resistance, wherein a cancer no longer responds to the therapeutic (see **Sidebar 35**, p. 87). The underlying mechanism of acquired resistance is multifactorial and is influenced by both extrinsic and intrinsic factors (480). Extrinsic factors include the tumor microenvironment (see **Tumor Microenvironment**, p. 35), and the presence of certain inhibitory immune cells that can change or accumulate over time. Intrinsic factors that lead to acquired resistance of a tumor include the downregulation of certain proteins on the surface of cancer cells that are required for the therapeutic to work. Identifying biomarkers that predict cancer recurrence is an area of active research. Utilization of combination therapy and strategies that target the tumor microenvironment are among the ways to overcome resistance and is another area of extensive investigation (see **A New Age of Therapeutic Combinations**, p. 130).

Finally, when a patient should cease receiving treatment with an ICI has not been well defined. This is because traditional endpoints, such as overall survival, progression free survival, and overall response rate, are not well-matched for assessment of ICIs (481,482). For instance, when measuring the overall response rate of a tumor to therapy, clinicians often examine tumor size before and after a treatment. Tumor shrinkage after therapy corresponds to a higher overall response rate. However, with ICI treatment, tumors often continue to grow before they shrink (e.g., pseudoprogression), which may initially be perceived as a lack of response (483). To overcome these limitations, criteria to define endpoints for ICIs have been developed (484); however, validation of these criteria will require large amounts of patient-derived data over a long period of time. Continued optimization and research for ICI endpoints must be developed to understand how long patients need to continue treatment.

Adverse Effects of Immunotherapy

Immunotherapeutics have led to more cancer survivors living through and beyond their cancer, with some patients remaining cancer free for 10 or more years. As the use of immunotherapy becomes more widespread, understanding the immediate and long-term adverse health impact of these therapeutics is crucial to improve health outcomes.

Cytokine release syndrome (CRS) is the most common immediate side effect following treatment with CAR T-cell therapy with a reported incidence of 37-93 percent

(453,485,486). CRS can develop within hours or days following infusion and is characterized by an excessive immune reaction that leads to widespread organ dysfunction that can become life-threatening (485). Following CRS, up to 40 percent of CAR T-cell recipients may develop another type of side effect called immune effector cell-associated neurotoxicity syndrome (ICANS), which can lead to neurological symptoms that affect speech, orientation, handwriting, and concentration (487).

While alarming, these side effects are often short-lived and readily managed with both corticosteroids and the IL-6R antagonist tocilizumab, approved by FDA to treat CRS in 2017 (488,489). Further evidence demonstrates that once a patient overcomes these symptoms, they do not recur (490).

A long-term side effect that has been observed in patients who receive CAR T-cell therapy targeting B-cell malignancies is depletion of normal B cells, called B cell aplasia. This condition arises when CAR T-cell therapy targets CD19, which is expressed not only on cancer cells but also on nonmalignant B cells, meaning that these cells can also be eliminated. B cell aplasia has been reported in 25-38 percent of patients for up to several years after conclusion of the treatment (491,492).

Other long-term side effects of CAR T-cell therapy include cytopenias, which are conditions in which there are lower than normal numbers of blood cells. Cytopenias include anemia (low red blood cells), thrombocytopenia (low platelets), and neutropenia (low neutrophils), and can occur in approximately 15 percent of patients with B-cell lymphoma more than three months after CAR T-cell infusion (493-496). Cytopenias persisted in long-term follow-up of 15–22 months in about 16 percent of patients (497).

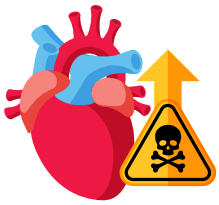
Other reported side effects, including increased risk of infection and malignant transformation of transduced cells are not well understood. Further complicating these findings is the difficulty of attributing these side effects to the treatment or the cancer itself.

The development of immune-related adverse events (irAEs), which are side effects from treatment with ICIs, can occur from the beginning of treatment and last well beyond its completion. The likelihood of someone treated with ICIs developing at least one irAE varies between 13.7 percent and 54 percent depending on the type of ICI (498).

Although they are often mild, ICI-induced irAEs can develop into more serious conditions that could become irreversible or even fatal (499). Many of these side effects are similar to autoimmune reactions, such as colitis, rash, or arthritis. These side effects have been documented in many organs and tissues (see **Figure 20**, p. 127).

Identification of new biomarkers is vital to better predict if a patient will develop irAEs, as well as to reduce the possibility of

ICI in combination with chemotherapy increased the risk of cardiotoxicity by 67 percent compared to chemotherapy alone in an analysis of patients with lung cancer across multiple studies (509).



these side effects. One promising area is examining whether the levels of certain immune cells in the body are associated with the development of severe irAEs. One study showed that levels of certain types of $CD8^+$ T cells could predict if a patient would develop arthritis following the administration of ICIs (see **Sidebar 38**, p. 100) (503). The presence of certain immune cells has also been associated with the development of side effects such as colitis, pneumonitis, and thyroiditis (503-505). Biomarkers in the blood could also be used to predict severe irAE, including cytokines such as IL-17, IL-6, and IL-8, all of which are elevated in patients who develop colitis following treatment with ICIs (505,506).

As patients treated with ICIs are living longer (507), it is important to note that although oncologists are generally aware of the potential for irAEs, this awareness is not as prevalent among primary care physicians who are a patient's first point of contact when seeking care. One study found that while 93 percent of physicians recognized the gastrointestinal tract was at risk for developing irAEs, only 57 percent recognized that the cardiovascular system and 67 percent recognized that the renal system was at risk following administration of ICIs (508).

With the increased use of immunotherapeutics resulting in improved survival, a better understanding of their long-term and late effects is urgently needed to improve quality of life for patients who receive immunotherapy.

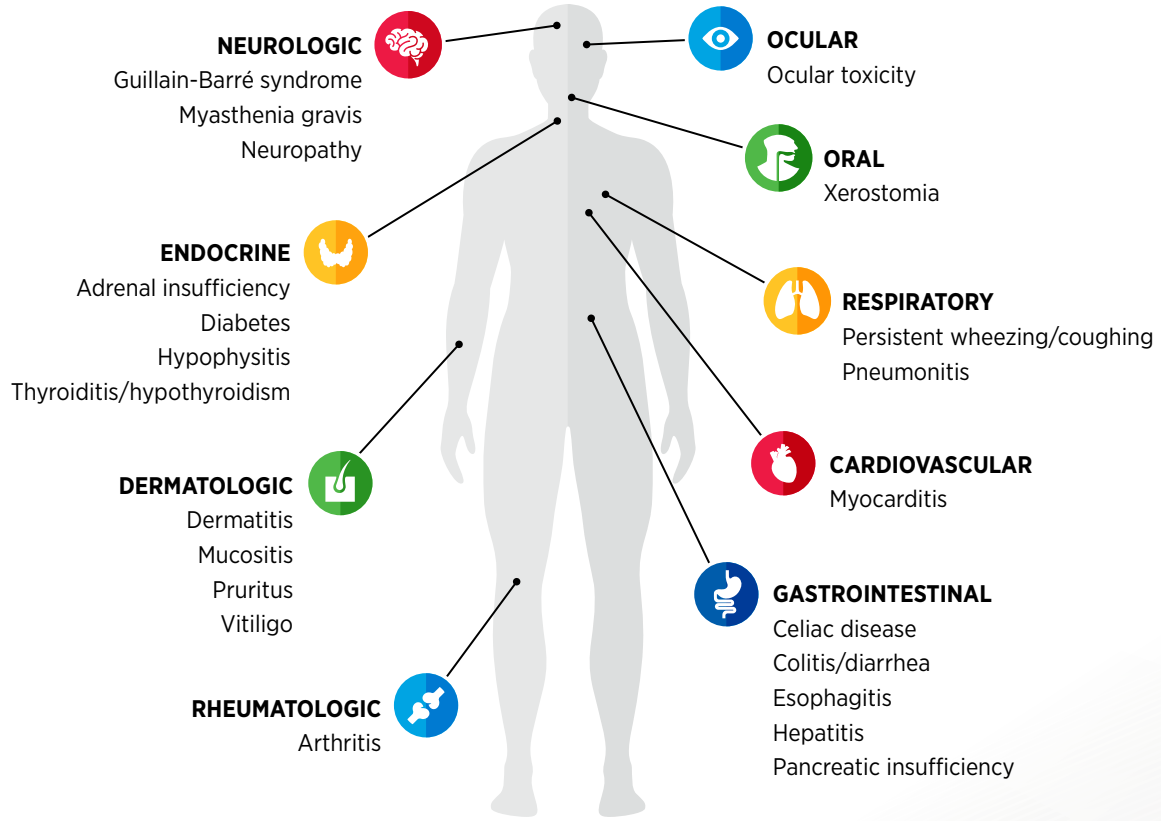
Disparities in Access to Immunotherapy

Emerging evidence shows that there are disparities in the access to immunotherapeutics, such as ICIs, particularly among racial and ethnic minority groups (see **Sidebar 2**, p. 17). One study of over 17,000 patients found that counties that were urban, had a higher proportion of Hispanic and Latino populations and higher poverty levels, had slower initiation of ICI therapy after diagnosis (510). The slow uptake of ICI occurred despite a higher density of cancer physicians, which indicates that the disparity was not exclusively due to lack of availability of appropriate care facilities.

Treatment of HCC, with immunotherapeutics was lower among both Hispanic and Black patients compared to White patients despite HCC having a higher incidence among Black and Hispanic populations (511, 512). This is especially

FIGURE 20

Common Side Effects of Immune Checkpoint Inhibitors



In 2011, the U.S. Food and Drug Administration (FDA) first approved a new type of immunotherapeutic called immune checkpoint inhibitors (ICIs), which are treatments that help the body recognize and attack cancer cells. Since then, the success of these treatments has led to many more people living longer, fuller lives after a cancer diagnosis. Only now are we seeing the long- and late-term side effects that can develop in patients treated with ICIs. The incidence of immune-related adverse events (irAEs) from ICIs depends on the drug being used and the tumor type; some of the most common irAEs are listed above (499-501).

Developed from (502).

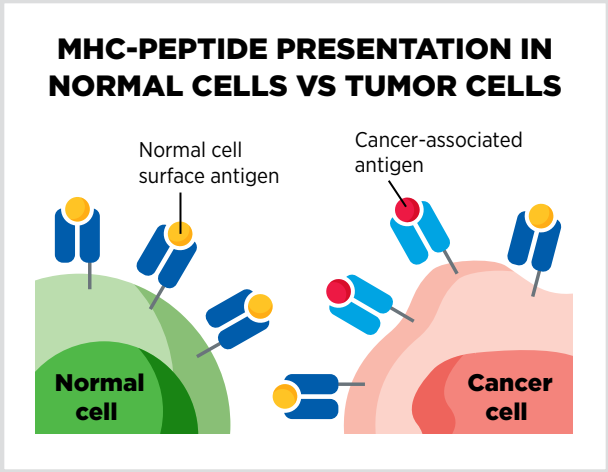
alarming because access to ICI therapy has been shown to improve overall survival compared to other types of treatment, such as chemotherapy (512).

There are also socioeconomic disparities in the access to immunotherapies. In a recent study examining immunotherapy use among patients with advanced-stage NSCLC, researchers found that having a low income and a lower level of educational attainment were associated with lower likelihood of receiving immunotherapy, and this persisted regardless of race or ethnicity (353).

There are also disparities in access to adoptive cell therapies. One study that evaluated the geographic distribution of CAR T-cell clinical trials for multiple myeloma found that 34 percent of states analyzed had no CAR T-cell or bispecific antibody clinical trial openings, with limited sites in states that have the highest percentages of Black residents (513). These data may explain why only two to five percent of participants in the pivotal clinical trials that led to the FDA approval of the CAR T-cell therapy tisagenlecleucel for ALL were Black (514).

Inequities in the current utilization of these highly effective therapies mandate further research to identify current barriers to the use of immunotherapy among medically underserved patients with cancer and to develop ways to address those barriers at the earliest possible time.

SPOTLIGHT



On the Horizon for Immunotherapy

As highlighted throughout this section, cancer immunotherapy has revolutionized cancer treatment and brought hope to countless patients with cancer who otherwise have no or limited treatment options. Thanks to research, progress in the field of immunotherapy is continuing at an unprecedented pace. Researchers are exploring several exciting new avenues to increase the number of cancer types that are treatable with immunotherapy, some of which are outlined in this section.

A New Era of mRNA-based Cancer Vaccines

Cancer vaccines work by boosting the magnitude of a patient's T cells with natural cancer-killing capacity. They do this by providing large amounts of the small pieces of cancer-specific proteins that T cells need to recognize on the surface of tumor cells in order to eliminate the cancer cells (515). Although the concept of cancer vaccines is not new, developing effective cancer vaccines has been challenging, as evidenced by the fact that, as of July 31, 2023, there is only one FDA approved therapeutic cancer vaccine (516).

The success of mRNA-based vaccines against SARS-CoV-2—the virus that caused the COVID-19 pandemic—has renewed interest in using mRNA-based vaccines to treat cancer (517). Furthermore, exciting new technological advances in sequencing DNA, RNA, and proteins are helping to catalogue abnormal proteins present in tumor cells that represent potential targets. Researchers are leveraging this knowledge to develop mRNA-based cancer vaccines that are tumor and patient specific.

The enormous potential of cancer vaccines is underscored by the findings of a recent study in pancreatic cancer, a particularly aggressive disease (518). Researchers developed an mRNA-based cancer vaccine that was tailored toward the abnormalities in the tumors in each of the 16 patients with pancreatic cancer who participated in the study. The vaccine stimulated an immune response against the cancer in half of the patients, and those who responded to the treatment did not have signs of cancer at the 18-months follow-up. These findings are extremely promising because pancreatic cancer has very low survival rate and very few treatment options (518). Another recent study evaluated the effectiveness of an mRNA-based vaccine for the treatment of metastatic melanoma. The results showed that the combination of the vaccine and the ICI pembrolizumab reduced the likelihood of cancer recurrence or death by nearly 44 percent compared to pembrolizumab treatment alone, which is a current standard of care for these patients (519).

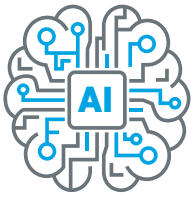
Cancer cells change constantly as cancer progresses (see **Understanding the Path to Cancer Development**, p. 24). As a result, the types of alterations in tumor proteins, as well as protein fragments present on the surface of tumor cells, also change. Advantages of mRNA-based cancer vaccines are that these therapeutics can induce responses to multiple targets, thus addressing heterogeneity, can be tailored against a patient's changing tumor, and can be produced rapidly (520). This latter capability allows researchers to periodically monitor which protein pieces are present on the surface of tumor cells of a patient, and to develop new versions of the vaccines that are more effective.

Therapeutic mRNA-based cancer vaccines have not yet been FDA approved for cancer treatment. However, a recent review of the early clinical studies evaluating the potential of mRNA-based vaccines in treating various types of cancer shows that findings from many of these ongoing studies are encouraging (521), and point to exciting new developments in this area of cancer medicine.

A New Generation of Immune Checkpoint Inhibitors

As discussed earlier, ICIs are one of the most widely effective cancer immunotherapies. As of July 31, 2023, FDA has approved 11 ICIs for the treatment of 20 cancer types (see **Figure 20**, p. 127). Although ICI treatment can lead to better long-term outcomes compared to other anticancer agents for certain patients, most patients do not respond to ICIs, and many who do respond at first eventually develop resistance to the treatment (522).

Researchers have developed an **artificial intelligence-based tool**, which uses the knowledge that blood vessels around tumors are often abnormal and **predicts the likelihood** with which the **tumor will respond to ICI treatment** (523).



Researchers are continually working to develop a much deeper understanding of additional immune checkpoint proteins and how they may be targeted alone or in combinations for cancer treatment. Progress in this area is reflected by the 2022 FDA approval of an ICI targeting a new immune checkpoint protein, called LAG-3 (1). Researchers are investigating the therapeutic potential of targeting other immune checkpoint proteins, such as B and T lymphocyte attenuator (BTLA) (524), T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3) (525), V-domain Ig suppressor of T-cell activation (VISTA) (526), and T-cell immunoreceptor with Ig and ITIM domains (TIGIT) (527), to unleash the immune system against tumors. Of these ICIs, researchers have identified TIGIT as one of the most promising new targets for cancer immunotherapy.

TIGIT is present on T cells and NK cells (see **Sidebar 38**, p. 100), and functions as a brake on the immune system. As one example, initial findings from an ongoing phase II clinical trial evaluating the potential of one such TIGIT inhibitor, tiragolumab, showed promising results in treating patients with lung cancer (528). In another phase II clinical trial, treatment of patients with stage IV lung cancer with a different TIGIT inhibitor, domvanalimab, showed improvement in progression-free survival (see **Sidebar 32**, p. 80) (529). It is important to note that these are still preliminary data and larger, randomized phase III studies are needed to establish whether TIGIT inhibitors will improve health outcomes for patients with cancer. There are currently 85 ongoing clinical studies evaluating more than 15 inhibitors of TIGIT at various phases of clinical development (530). Findings from these and future studies will provide further insight into the effectiveness of TIGIT inhibitors in cancer immunotherapy.

Researchers are also evaluating ICIs that can release the brakes on other types of immune cells beyond T cells and unleash them against cancer. As one example, research has shown that macrophages (see **Sidebar 38**, p. 100) have a protein, called signal regulatory protein α (SIRPα), on their surface. SIRPα functions as a brake on macrophages and stops them from killing microorganisms, removing dead cells, or activating other immune cells. Interestingly, many tumor cells have high amounts of a protein, called CD47, on their surface, which binds to SIRPα, and sends the "do not eat me" signal to macrophages (531). Ongoing research is focused on developing drugs that can release the interaction between the two proteins and activate macrophages against different types of cancer (532,533).

A New Wave of Adoptive Cell Therapeutics

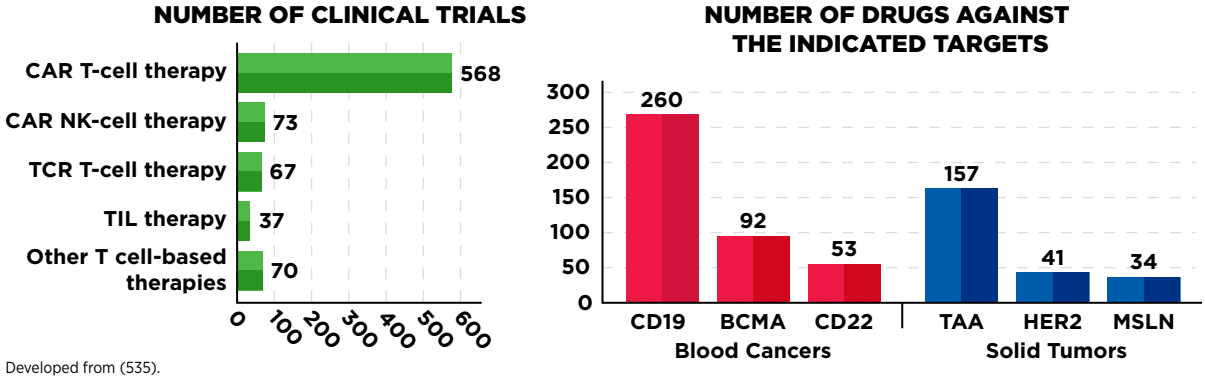
While all of the ACTs currently approved by FDA are based on CAR T cells (see **Sidebar 40**, p. 117), extensive ongoing research is exploring the utility of other ways to modify T cells (534), as well as of other types of immune cells as anticancer agents.

One group of immune cells with therapeutic potential against cancer are called natural killer (NK) cells. NK cells act rapidly and directly to kill infected, damaged, or cancer cells by releasing toxic compounds. This efficiency and speed of killing unwanted cells make NK cells an ideal candidate for developing effective immunotherapeutics.

Compared to the currently approved CAR T-cell therapies, immunotherapeutics based on NK cells have several advantages including relatively better availability (NK cell-based treatments do not necessarily rely on cells isolated from patients; cells could potentially be isolated from healthy individuals), comparatively shorter time to be available for therapy (NK cells can be prepared and stored for later use), and potentially fewer side effects (536). Similar to the T-cell based immunotherapies, therapies based on NK cells are developed against proteins present on the surface of cancer cells which helps NK cells recognize cancer cells and kill them. However, NK cells lack many of the advantages of T cells,

GLOBAL LANDSCAPE OF ADOPTIVE CELL THERAPIES IN CLINICAL DEVELOPMENT IN 2022

As of April 5, 2022, there are 2,756 active cell therapy agents in clinical development globally.



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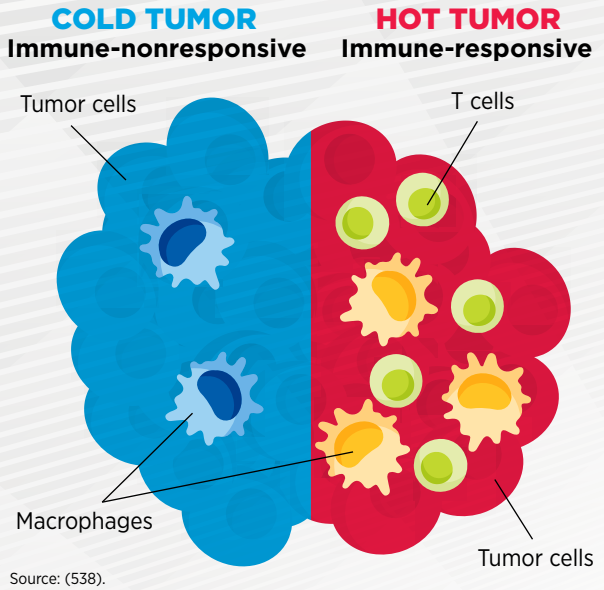
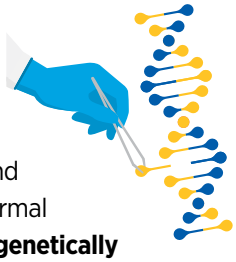


Source: (538).

including the abilities to significantly expand upon recognizing their target and to form long-term memory, and don't have the fine specificity of T cells. Currently, several NK cell-based immunotherapeutics to treat many types of cancer are at various stages of clinical development (537).

Another group of immune cells with great potential as an immunotherapeutic are tumor-infiltrating lymphocytes (TILs). These cells are present inside the tumor microenvironment and can recognize and kill cancer cells (see **Tumor Microenvironment**, p. 35).

In TIL therapy, researchers remove a portion of the tumor from a patient, isolate TILs from it, grow them in large numbers quickly, and infuse them back into the patient (see **Sidebar 39**, p. 116). In early clinical studies, TIL therapy has shown remarkable success in a number of cancer types, including melanoma and cancers of the cervix, colon and rectum, bladder, lung, and breast (539). As one example, cancer-free survival more than doubled in patients with advanced skin cancer who received TIL therapy, compared to those who received standard of care treatment (540).



Researchers used **precision genome editing** to modify healthy T cells so that the cells were targeted against a patient's cancer, and did not attack the body's normal cells. **Administration of the genetically modified T cells completely eliminated leukemia in a 13-year-old patient**, who is one of the first 10 patients to receive this cutting-edge cancer treatment (544).

It is also noteworthy that, compared to the currently approved CAR-T cell-based ACT, both NK cell-based and TIL immunotherapeutics have shown greater success in treating solid tumors. An exciting new approach is to combine the power of ACTs with technological advances in genetic engineering to target specific mutations present in a patient's tumor. There are several advantages to this approach, including personalizing the treatment to the patient's tumor, increasing the time the engineered immune cells can stay in the body, and reducing their ability to fight a patient's normal cells (541). Engineered T cells with T-cell receptors (TCRs) targeting tumors with mutations in cancer-driving genes, such as KRAS (542), have already shown efficacy in patients, and more trials using newly isolated TCRs specific for such targets are poised to begin in 2023 (543).

With technological advances and increased knowledge of immunology, the field of ACT is on the verge of unleashing the potential of the immune system even further for the benefit of patients with cancer.

A New Age of Therapeutic Combinations

Precision medicine approaches including immunotherapy and molecularly targeted therapy have transformed the landscape of cancer care. However, only a fraction of patients responds to these treatments, and most tumors eventually develop resistance to current treatments (see **Sidebar 35**, p. 87) (545). To address these challenges, researchers are evaluating combinations of therapeutics within and between various treatment modalities, such as immunotherapy, molecularly targeted therapy, and radiotherapy, in many clinical trials against a wide array of cancers. There is already emerging evidence that combination therapy is an effective way to overcome or delay the development of resistance (546).

Immunotherapeutics, especially ICIs, have shown remarkable success when used in combination with other methods of treating cancer. The success of using immunotherapeutics in combination is underscored by several FDA approvals of drug combinations to treat different types of cancer. Research has shown that the best outcomes are achieved when therapeutics are combined rationally based on their underlying mechanisms of action (547).

Among the most promising of combinations are those that combine an immunotherapeutic with a molecularly targeted therapeutic or two different immunotherapeutics (549). Treatment with ICIs has also been effective when given before the surgery to remove the tumor (to shrink the tumor size and kill cancer cells that have spread in the body) (550), or after the tumor is surgically removed (to kill remaining

SIDEBAR 41

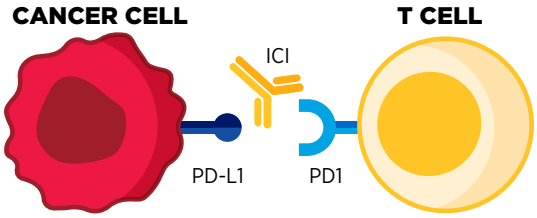
SPOTLIGHT

Clinical Trials Testing Immunotherapy Combinations with Other Modalities

Ongoing research is evaluating the effectiveness of combining immunotherapy with other types of cancer treatments. Here we highlight selected examples of immune checkpoint inhibitor combinations with other types of cancer treatments.

CANCER TYPE	CLINICAL TRIAL PHASE	COMBINATION	TREATMENT GROUPS	IMPACT OF COMBINATION
Advanced HER2-positive gastric cancer (553)	III	**Immunotherapy** + **molecularly targeted therapy** + **chemotherapy**	pembrolizumab + trastuzumab + chemotherapeutic **versus** trastuzumab + chemotherapeutic	Improved overall response
HER2-negative stage II/III breast cancer (553)	II	**Immunotherapy** + **molecularly targeted therapy** + **chemotherapy**	durvalumab + olaparib + paclitaxel **versus** paclitaxel	Improved partial response rate
Metastatic triple negative breast cancer (554)	III	**Immunotherapy** + **chemotherapy**	pembrolizumab + chemotherapy **versus** chemotherapy	Increased overall survival
Non-small cell lung cancer; carcinoma (555)	II	**Immunotherapy** + **radiation therapy**	pembrolizumab **versus** pembrolizumab + radiation therapy	Improved overall survival

As of December 2021, **4,062 clinical trials** (83 percent of all 4,897 active trials) were testing **ICIs targeting PD-1/PD-L1 proteins** in combination with other immunotherapies, molecularly targeted therapies, chemotherapies, and radiotherapies (548).



tumor cells) (551), as well as when given in combination with chemotherapy or radiotherapy (549). Furthermore, researchers are investigating whether combining immunotherapeutics with modulation of the patient's microbiome (see **Targeting the Microbiome in Cancer Treatment**, p. 150) will further increase their effectiveness in treating cancer (552).

Currently, there are many therapeutic combinations being tested in clinical studies (see **Sidebar 41**, p. 131).

Researchers are continually pioneering different methods to identify and test novel therapeutic combinations that may be more effective and safer to treat cancer, and/or may be able to overcome or delay resistance to cancer treatment. Given that the number of potential combinations of therapies is immense and will increase dramatically as the number of cancer treatments rises in the future, continued research is needed to identify biomarkers to help determine the most effective combinations. Researchers anticipate that big data approaches and machine learning technologies will further accelerate the pace of research in combination therapy for cancer. Mechanism-based rational combinations of different immunotherapeutics or with other treatment modalities have the potential to transform the future of cancer care.

Supporting Cancer Patients and Survivors

IN THIS SECTION, YOU WILL LEARN:

- As of January 2022, the most recent year for which such data are available, there were more than 18 million people living in the U.S. with a history of a cancer diagnosis and this number is expected to rise to 26 million by 2040.
- A cancer diagnosis has a lasting impact on survivors that brings a host of challenges including numerous short- and long-term side effects related to cancer and its treatments.
- Children, adolescents and young adults, and older adults who have survived cancer face unique and/or exacerbated challenges.
- Physical activity, a healthy diet, and smoking cessation are all proven ways to improve survival and quality of life.
- Patient navigators, clinical care coordinators, and patient advocates can enhance patient outcomes by improving a cancer survivor's mental and physical health.

According to NCI, a person is considered a cancer survivor from the time of cancer diagnosis through the balance of his or her life. Each person diagnosed with cancer has a unique experience ranging from successful treatment and living cancer free for the remainder of life to experiencing varying degrees of side effects and/or a subsequent cancer diagnosis with the same or a different type of cancer.

Unprecedented advances in cancer treatments over the past decade have led to more patients living longer and fuller lives after a cancer diagnosis. As of 2022, the most recent year for which such data are available, there are 18.1 million people living with a history of a cancer diagnosis, which equates to about five percent of the U.S. population (7). This is a significant improvement from 50 years ago when cancer survivors constituted only 1.4 percent of the U.S. population. The number of survivors is expected to grow to 26 million by 2040. Understanding and addressing the short- and long-term challenges faced by cancer survivors, supporting their quality of life, and ensuring that care is accessible and equitable are important priorities in cancer survivorship research (7).

A cancer diagnosis also impacts friends, family members, and caregivers, who are often the main support network for the survivor. This necessitates widening the focus of research, support, and care beyond the cancer patient and survivor to include individuals who make up the support structure.

Between 2013 and 2019, the **number of cancer survivors diagnosed with a new malignancy** increased 15 percent (556).

Among cancer survivors from 2007 to 2016, those who lived in metropolitan counties had a **1-year survival rate** of 81.1 percent compared to 77.8 percent in nonmetropolitan counties (557).

The following section highlights the challenges faced by cancer survivors and their support network, strategies to improve quality of life, and approaches that have been shown to deliver care most effectively.

Challenges Faced by Cancer Survivors

Cancer survivors often face physical, psychosocial, and financial challenges throughout their survivorship journey. The number of cancer survivors living with a functional limitation, defined

as difficulty performing any of 12 routine physical or social activities without assistance (e.g., sitting for more than two hours or participating in social activities) more than doubled from 3.6 million in 1999 to 8.2 million in 2018 (558). The functional limitations can vary based on the type of cancer diagnosed and were highest among survivors of pancreatic cancer (80.3 percent) and lung cancer (76.5 percent) and lowest for those who had melanoma (62.2 percent), or cancers of breast (61.8 percent) and prostate (59.5 percent) (558).

While cancer researchers and physicians have learned a lot about these challenges over the years, implementation of groundbreaking new treatments, such as immunotherapies, presents unique short- and long-term challenges that are only beginning to be understood (see **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99). A greater understanding of these challenges and ways to address them is urgently required to support cancer survivors.

Physical Challenges

Survivors can experience a wide range of short- and long-term symptoms caused by cancer or its treatments. Short-term effects include hair loss, pain, nausea, vomiting, and loss of smell and appetite with varying severity of symptoms depending on the person, cancer type, and treatment. As cancer survivors are living longer due to better therapies, the development of long-term side effects such as heart damage (cardiotoxicity), lung damage, loss of bone density, and cognitive decline is becoming more common and demands a greater understanding to reduce or manage these conditions (see **Sidebar 42**, p. 134).

Cachexia is the loss of body weight and muscle mass, and weakness that may occur in patients with cancer or other chronic diseases. Cachexia is estimated to occur in up to 80 percent of patients with advanced cancer. For instance, cachexia occurs in 87 percent of patients with pancreatic and gastric cancers, and in 61 percent of patients with NHL or with cancers of the colon and rectum, lung, and prostate. The development of cachexia indicates poor prognosis and accounts for 20 to 30 percent of all cancer-related deaths. Loss of muscle, especially heart and skeletal muscle, leads to widespread disturbances in biological functions (559). In patients with metastatic cancer, who are at the highest risk for cachexia, reduced nutrient intake coupled with high energy demand caused by cancer and its side effects results in a negative energy balance. In some instances, pain management can help to increase appetite, which can slow the advancement of cachexia (560). Understanding the biological underpinnings and addressing cancer-related cachexia are areas of ongoing basic and clinical investigation (561).

Chemotherapy-related cognitive impairment, often termed as "chemo brain," has been reported by many cancer survivors to describe thinking and memory problems before, during, and after cancer treatment. Accumulating evidence from brain imaging studies shows the biological effects of cancer therapeutics on the brain, including changes in glucose consumption, blood flow, and expression of certain proteins (562), all of which may contribute to cognitive impairment. Many survivors report having increased cognitive impairment even after a year following the completion of cancer treatment, indicating these effects can be long-standing (563).

Severe immune-related adverse events occur in **up to 60 percent** of patients with melanoma **treated with immune checkpoint inhibitors** (566).

Cardiotoxicity from certain types of anticancer therapeutics has been reported in many studies and increases the risk of clinical hypertension, coronary artery disease, heart failure, and atrial fibrillation, among others. Research has also shown that cancer survivors have an "excess heart age"—a measure of cardiovascular damage and risk of a heart attack—compared to individuals who have never received a cancer diagnosis. Studies of cancer survivors have shown an excess heart age of eight and a half years in men and six and a half years in women (564). Furthermore, there are disparities in severity of adverse cardiac events among cancer survivors. Non-Hispanic Black cancer survivors had higher rates of cardiovascular disease-related mortality compared to Hispanic, non-Hispanic Asian/Pacific Islander, and White patients (565).

Immunotherapies, including immune checkpoint inhibitors and adoptive cell therapies, are still a relatively new class of treatment compared to other types of cancer therapies. Their long- and late-term side effects are being studied as successful treatment with these therapeutics has led to many more people living longer (see **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99).

Psychosocial Challenges

A diagnosis of cancer can pose serious challenges to a person's mental and emotional health. Based on recent data, one in six patients with cancer has pre-existing psychiatric conditions, which can lead to longer hospital stays, higher rates of readmission, and increased risk of suicidal thoughts after the treatment ends in patients undergoing surgery for their cancer (567). Many survivors experience anxiety (7 to 21 percent of patients), depression (8 to 24 percent of patients), and distress (25 to 41 percent of patients) following the completion of cancer treatment (13,568-570). A study that examined 26 different cancer types found that 98 percent of patients with testicular cancer, 78 percent of patients with cervical

SIDEBAR 42

Phases of Cancer Survivorship

Survivorship is a continuum that can be broken down into three phases as shown below. Which phase a survivor belongs to depends on the treatment received, type and stage of cancer, and goal of care as determined by patient and care provider. It is important to note that some survivors of metastatic cancer continue to remain on active treatment for the rest of their lives to keep their cancer under control.

Phases	Acute Survivorship (Time of diagnosis – End of Initial Treatment)	Extended Survivorship (End of Initial Treatment – End of Initial Assessment)	Permanent Survivorship (End of Initial Assessment –)
FOCUS	Cancer treatment	Immediate effects of cancer and treatment	Long-term effects of cancer and treatment
DURATION	Several weeks	Several months	Several years
CHALLENGES	• Bone density loss (osteoporosis) • Cachexia and/or sarcopenia • Cognitive impairment (trouble remembering, learning new things, concentrating, and/or making decisions that affect everyday life) • Diagnosis with a new type of cancer(s) • Distress, anxiety, and/or depression, which can interfere with a person's ability to cope effectively with cancer and its treatment • Endocrine dysfunction, which is dysfunction of the collection of organs and glands that control body functions such as growth, sexual development, reproduction, sleep, hunger, and the way the body uses food • Fatigue that is severe and often not relieved by rest • Fear of cancer recurrence • Hearing loss • Heart damage (cardiotoxicity) • Infertility		• Insomnia • Joint changes • Lung (pulmonary) damage • Lymphedema, which is swelling, most often in the arms or legs, that can cause pain and problems in functioning • Metabolic syndrome, which occurs when an individual has three or more of the following health risk factors: excess body fat around the waist, high blood pressure, high triglycerides, impaired fasting glucose, and low HDL cholesterol • Nerve problems (including peripheral neuropathy) • Nutrition issues • Oral changes • Pain • Premature aging • Recurrence (return) of original cancer • Sexual dysfunction
HOW TO COPE	• Build a close circle of support • Manage pain by medication and/or meditation • Adopt a healthy lifestyle • Learn about psycho-oncology and see if it can help you cope with anxiety		• Join a cancer support group • Use mindfulness to cope with long-term effects of cancer treatment • For more information, visit: https://www.cancer.gov/about-cancer/coping

Although cancer survivors may face challenges, some groups are at higher risk for severe and long-term and late effects. This includes those diagnosed during childhood, adolescence, and young adulthood (from ages 0 to 39). Several organizations have established guidelines specifically for adolescent and young adult patients including National Comprehensive Cancer Network's (NCCN) "Adolescents and Young Adults with Cancer" and The Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers." These guidelines were developed to help standardize and enhance the lifelong follow-up care of individuals who were diagnosed with cancer as children, adolescents, or young adults. For more information, see **http://survivorshipguidelines.org/**.

This also includes older adults (age 65 and older). The NCCN's "Guidelines for Older Adult Oncology" address specific issues of cancer in older adults, including screening and comprehensive geriatric assessment, treatment risk and benefits, and management of complications from therapies.

Suicide risk was found to be **higher in patients with cancer undergoing surgery** compared to the general population, with approximately 50 percent of suicides being committed within the first three years after surgery (572).

The National Suicide Prevention Lifeline has established a new **three-digit telephone number, 988**, to provide **free and confidential support** for those experiencing thoughts of suicide or distress.

cancer, and 69 percent of patients with Hodgkin lymphoma experienced a depressive event (570). Psychological distress is more prevalent among those who are AYA or belong to a racial and ethnic minority (13,568-570). Those who belong to sexual and gender minority populations are also at a greater risk of having lower psychological well-being, which is exacerbated in cancer patients living with HIV (571).

Controlling depression can improve survival, with a recent study showing that 1-year survival in patients with cancer whose depression symptoms improved was 64 percent versus only 42 percent for those whose symptoms worsened (573). Emerging evidence suggests that the level of depression directly correlates with the degree of systemic inflammation in patients with cancer as measured by immune system markers, such as levels of cytokine or certain immune cells (574-576). For example, patients with lung cancer with moderate to severe depression were two to three times more likely to have inflammation levels that predict poor survival rates. Immune system dysregulation may also lead to a poor response of these patients to immunotherapies, which rely on a functional immune system to be effective.

Systemic inflammation occurs when the immune system is constantly active due to stress, infection, or chronic disease. This condition has been **shown to alter the blood-brain barrier**, which controls what type of cells and chemicals can reach the brain (577).

Financial Challenges

Financial toxicity refers to the financial hardship associated with cancer treatment and management. Evidence indicates that cancer survivors who experience financial toxicity such as difficulty paying for prescriptions, mental health care, and other health services, and/or who delay medical care due to cost, are also at greater risk of mortality, regardless of insurance status (578).

Financial toxicity is pervasive and is, in part, exacerbated by the rising cost of cancer care (480). For instance, between 2009 and 2016, the average cost of treatment increased 29 percent for breast cancer, 11 percent for lung cancer, and four percent for prostate cancer. In addition, out-of-pocket costs have also increased by 15 percent for all patients with cancer (579).

Survivors can face challenges maintaining a job or going back to a previous job after the conclusion of treatment. Cancer survivors between the ages of 50 and 64 years were more likely to have a work-limiting disability and less likely to be employed, equating to 505,768 fewer employed individuals between 2010 and 2016 (580).

In 2021, **78.8 percent** of patients with **breast cancer** in **low- and middle-income countries** and 35.3 percent in high-income countries experienced financial toxicity (581).

Apart from direct financial costs, it is also common for cancer survivors to have housing, food, and transportation insecurity. As a result of these challenges, patients may forgo, miss, delay, alter, and/or prematurely terminate necessary care (582-584). Food insecurity is pervasive among people navigating a cancer diagnosis, with anywhere between 17 and 55 percent of patients with cancer facing food insecurity (584). This may explain why cancer survivors are more likely to be on supplemental nutrition assistance programs (SNAP) than the general population (580).

Caregivers of patients with cancer are also susceptible to many of the same challenges faced by the patients. Lost income due to taking time off or leaving their employment can increase susceptibility to financial toxicity. For instance, 68.1 percent of partners of those diagnosed with colorectal cancer reported adverse financial outcomes following diagnosis, which led to worsening of health-related quality of life for these caregivers (585). Another study found that cancer caregivers from lower socioeconomic backgrounds were more likely to increase debt and incur work loss compared to noncancer caregivers in similar households (586).

35 percent of cancer caregivers reported that they **stopped working to provide care** to someone diagnosed with cancer (586).

Unique Challenges Faced by Vulnerable Patient Populations

Children

Pediatric or childhood cancers are those diagnosed from birth until the age of 14 years. In the United States in 2023, an estimated 9,910 new cases of cancer will be diagnosed among children. Thanks to major treatment advances, 85 percent of children are expected to live five years or more after a cancer diagnosis. This is a marked improvement compared to the mid-1970s, when only 42 percent of children lived beyond five years after a cancer diagnosis (587). Because childhood cancer survivors are diagnosed at a young age, they will be living longer postdiagnosis than an adult who has been diagnosed with cancer.

The degree and type of late-stage side effects childhood cancer survivors develop depend on a variety of reasons, including the type and stage of cancer at the time of diagnosis, the type and dose of treatment, and the age and general health of the patient at the time of treatment. Reports indicate that 60 to 90 percent of childhood survivors develop one or more chronic health conditions following their cancer diagnosis (588,589).

Pediatric patients who receive chemotherapeutics are at an increased risk of developing hearing loss, also called ototoxicity. One study found that 75 percent of children under five and 48 percent of children over five who were treated with cisplatin had hearing loss related to their treatment (590). In September 2022, FDA approved sodium thiosulfate to reduce the risk of hearing loss associated with the chemotherapeutic cisplatin in pediatric patients one month and older. Sodium thiosulfate reduced the risk of cisplatin-associated hearing loss by almost 60 percent compared to those who did not receive the drug (591). By preventing ototoxicity, this approval will help many pediatric cancer survivors experience a better quality of life.

5-year survivors of childhood cancer **reduced their risk of health-related mortality** by 20 to 30 percent when **adhering to a healthy lifestyle** (592).

Pediatric cancer survivors are also more susceptible to premature aging. According to one study, daily functional limitations, psychosocial symptoms, and health conditions of a 30-year-old cancer survivor are similar to those of a 63-year-old healthy individual (593).

While premature aging and cancer is an emerging research area, new evidence implicates changes in the epigenome that occur after treatment with cancer therapies as a contributing factor. In one study that evaluated changes in the epigenome of adult survivors of childhood cancers, researchers identified epigenetic patterns that are normally found in much older individuals. These changes were directly associated with the development of early-onset obesity, chronic health conditions, and higher risk of dying within 5 years (594).

The quality of mental health among survivors of childhood cancers is also concerning. When compared to their healthy siblings, young adult survivors of childhood cancers reported increased loneliness that subsequently increased anxiety, depression, and the likelihood of smoking. Long-term follow-up with these patients found higher levels of suicidal thoughts, and heavy/risky alcohol consumption (569). This population is also more susceptible to major mental health illnesses, including autism, attention deficit disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and posttraumatic stress disorder, with the greatest number of mental health illnesses experienced by survivors of brain and lymphatic/hematopoietic tissue cancers (595).

Adolescents and Young Adults

Adolescent and young adult (AYA) cancer survivors are those diagnosed between the ages of 15 and 39. Based on estimates of new cancer cases in 2023, 4.4 percent of all new cases will be in AYA and 85.8 percent of AYAs diagnosed with cancer will live 5 years or more after their diagnosis (596). This population group faces unique personal, social, and emotional challenges.

Many AYA survivors experience long-term side effects and are at a two- to three-fold higher risk of premature ovarian failure, chronic liver disease, renal failure and cardiovascular disease compared to those with no diagnosis of cancer (597).

Between 44 and 86 percent of AYA survivors have concerns regarding how treatments for cancer, including surgery, radiotherapy, and cytotoxic chemotherapy, may lead to infertility, which is the inability to conceive a child (598). The possibility of impaired reproductive abilities may lead some patients to store reproductive material through the process of fertility preservation (see **Sidebar 43**, p. 137). Participation in fertility preservation and the type of preservation should be decided by the individual after discussions with his or her health care providers.

SIDEBAR 43

Fertility Preservation After a Diagnosis of Cancer

One of the adverse consequences of cancer treatments is infertility or the inability to conceive a child. This may result from surgery on reproductive organs or effects of cancer medications on reproductive cells, and can affect both male and female patients. Thus, those diagnosed with cancer should consider discussing with their health care providers whether infertility is a risk for them. If so, the discussion should include whether fertility preservation is an option and which of the available options should they consider.

BOYS AND MEN:

- Sperm banking
- Shielding of testes from radiation if receiving radiotherapy

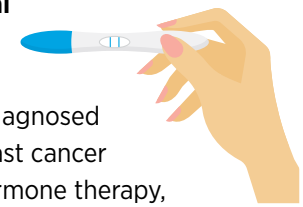
GIRLS AND WOMEN:

- Banking of ovarian tissue
- Banking of eggs
- Banking of embryos
- Surgically moving ovaries away from areas of radiotherapy
- Removing cervix but preserving uterus
- Shielding of ovaries from radiation if receiving radiotherapy

Unfortunately, fertility preservation rates are lower in survivors who are Black, poor, or live in rural areas. Currently, cancer-focused organizations have guidelines that recommend discussions of fertility preservation and sexual health as an essential part of cancer management, especially in AYA patient populations. Furthermore, as of July 2023, 16 states have mandates, and three have active legislation, requiring insurance coverage of fertility preservation for patients facing infertility due to treatments such as anticancer therapies (599). This is an increase from July 2022, when only 12 states had mandates.

Receiving a diagnosis of cancer during pregnancy, which may occur for AYAs, raises questions about how cancer treatment may affect both the mother and the developing embryo or fetus; about one in 2,000 pregnancies is complicated by cancer according to estimates (600). The risk to mother or offspring from cancer or the treatment of cancer is mixed and is dependent on a multitude of factors such as age, cancer type, stage of cancer, the trimester at diagnosis, and therapy type received (601-603).

The **POSITIVE clinical trial** found that women under the age of 43, who are diagnosed with early-stage breast cancer and are receiving hormone therapy, **can safely pause their treatment** for up to two years **without increasing** the **risk of cancer recurrence or decreasing the likelihood of becoming pregnant** (604).



AYAs also have worse mental health outcomes compared to those without a diagnosis of cancer. AYA cancer survivors had an 80 percent increased risk of hospitalizations for mental health illnesses and were 4.5 times more likely to purchase antidepressants compared to their siblings (605). Furthermore, a subset of AYA survivors is at risk for early death, with those diagnosed with hematologic malignancies facing the highest risk (606).

Financial toxicity among AYA cancer survivors is also higher compared to those with no diagnosis of cancer. One study reported that the costs associated with a diagnosis of cancer are substantial, reaching an average of $259,324 per person over their lifetime. One reason is that a cancer diagnosis often affects these individuals when they are just beginning higher levels of education or starting careers, potentially impacting productivity and well-being (54).

The Affordable Care Act (ACA) resulted in improved insurance coverage. Evidence is emerging that states which expanded Medicaid under the ACA had improved overall survival among young adults with cancer, specifically among racial or ethnic minorities when compared to states that did not expand Medicaid benefits (608).

In an **analysis of AYA survivors**, 71 percent indicated that they faced at least one barrier to survivorship care. These barriers were increased in **non-Hispanic Black survivors**, with 92 percent reporting difficulties in accessing survivorship care (607).

Older Adults

Older adults are defined as those age 65 and over, representing 64 percent of cancer survivors in the United States. This population is also the fastest growing and is projected to increase to 73 percent of cancer survivors by 2040 (609).

Cachexia is common among older cancer survivors, especially among those with gastrointestinal cancers; an estimated 52 to 65 percent of older cancer survivors develop cachexia (610,611). Specifically, loss of muscle mass and strength, called sarcopenia, occurs in 12.5 to 57.7 percent of adult cancer survivors (612-615).

Fracture risk due to bone density loss (osteoporosis) is becoming another increasing concern in this demographic. In one study of older adults with a mean age of 69 years, researchers found that cancer survivors diagnosed within the last five years had two times the risk of bone fracture compared to those with no history of cancer. It is important to note that higher fracture risk was positively associated with current smoking status (616). Older adults may benefit from programs, such as physical therapy and smoking cessation, that are shown to reduce the risk of fracture (617).

Research into older cancer survivors and their unique risks is important as the U.S. population ages, life expectancy increases, and cancer survivorship rises.

Improving Health-related Quality of Life and Outcomes

Promoting Healthy Behaviors

Healthy behaviors, such as physical activity, a healthy diet, reduced alcohol consumption, and smoking cessation, can significantly improve both health outcomes and health-related quality of life (HRQOL) for cancer survivors. In fact, it is increasingly appreciated that adopting healthy behaviors after a diagnosis of cancer but prior to beginning cancer treatment, called prehabilitation or "prehab" can significantly improve outcomes for patients. A patient who is healthy at the start of treatment can undergo higher doses of drug, is less susceptible to certain side effects, and has an immune system that is primed to fight cancer better.

Physical activity has been shown to increase survival and lower recurrence of cancers (618). Physical activity changes how organs and tissues function to resist both cancer progression and/or metastasis. Because the body requires energy (in the form of carbohydrates, such as glucose), increasing physical activity levels increases the demand for energy from organs. One study found that by increasing physical activity levels, the amount of energy that was available to tumors was reduced because it was needed by the rest of the body during physical activity. Participants who were more active had lower rates of metastatic progression compared to those who were not active (175).

In breast cancer survivors, **moderate exercise** is associated with a **60 percent lower risk of death** (621).

Physical activity can also improve treatment outcomes. A meta-analysis of breast cancer survivors who underwent curative treatment found that frequent physical activity improved HRQOL, cardiorespiratory fitness, and body composition (619). A second study showed that in a group of patients who underwent radiotherapy for breast cancer, biweekly aerobic exercise sessions of 30 to 40 minutes each significantly improved cancer-related fatigue and HRQOL (620).

Research has shown that sustaining a healthy diet that consists of whole grains, fruits, and vegetables can increase survival from cancer and reduce the risk of cancer recurrence (622). Cancer survivors who adhere to a high-quality, balanced diet have better quality of life, mental well-being, and survival (623-626). Diet is also important for maintaining a healthy gut microbiome, which is the collection of organisms that occupy the intestines and aid in digestion (see **Targeting the Microbiome in Cancer Treatment**, p. 150).

Smoking among cancer survivors is associated with poor outcomes and greater treatment-related complications, higher risk of secondary cancers, and greater mortality (123). Smoking cessation is a crucial intervention that can improve clinical outcomes during and after the completion of cancer treatment (627). Many cancer-focused professional organizations strongly recommend smoking cessation after a cancer diagnosis. Evidence demonstrates that the most successful methods include involving a trained tobacco specialist who can screen patients and assist them in achieving abstinence; improving clinician education on how to deal with and refer patients appropriately; and building relationships with implementation stakeholders (628).

Integrating Palliative Care

Palliative care is an approach to prevent or treat the symptoms and side effects of any disease, including cancer, by addressing the physical, psychosocial, financial, and spiritual needs that arise from the disease and treatments (see **Sidebar 44**, p. 139). Palliative care is facilitated by multidisciplinary teams of doctors, nurses, dieticians, pharmacists, therapists, spiritual leaders, and social workers and has been shown to improve quality of life for patients, families, and caregivers.

SIDEBAR 44

What Is Palliative Care?

Palliative care is specialized care that provides, if needed, an extra layer of support to patients with and survivors of serious illnesses, such as cancer, and their families and caregivers.

Palliative care is given throughout a person's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care. Palliative care given near the end of life when curative treatment has stopped is usually referred to as hospice care.

Palliative care can be given in addition to cancer treatment or to those with no curative treatment options. Palliative care addresses many of the challenges that can affect quality of life after a cancer diagnosis, including:

- Emotional challenges, such as anxiety and depression.
- Physical symptoms and adverse effects of the disease and its treatment, such as pain, nausea, vomiting, fatigue, difficulty sleeping, and loss of appetite.
- Practical challenges, such as navigating the health care system.
- Spiritual challenges.

Adapted from (389).

Studies show that integration of palliative care through consultation with a palliative care team early on after cancer diagnosis is most effective in improving HRQOL, increasing satisfaction with care, and mitigating depression (629-631). For patients with advanced cancers, including those with solid and blood cancers, ongoing consultation with a palliative care specialist throughout treatment led to improved communication between patients, caregivers, and the clinical care team leading to an overall increase in life expectancy (632).

Palliative therapy, which aims to relieve symptoms of cancer through surgical or therapeutic intervention, can also improve quality of life for patients. As one example, patients with gastric cancers, who develop complications in advanced stages of the disease, can benefit from gastric resection, gastrojejunostomy, stenting, chemotherapy, and radiotherapy, which reduce gastric obstruction and bleeding, and improve patient quality of life (633).

SIDEBAR 45

Helping Patients with Cancer Through Psycho-oncology Research

The field of psycho-oncology comprises psychiatrists, psychologists, nurses, and social workers who are dedicated to addressing the behavioral, emotional, psychological, and social challenges faced by cancer survivors and their caregivers. Approaches to helping these individuals tested in recent clinical trials include:

Physical exercise (aerobic, resistance training, running, and free weights), **psychological interventions** (cognitive-behavioral therapy, psychoeducational interventions), **and mind-body interventions** (yoga, mindfulness, hypnosis) have been shown to be effective at reducing cancer-related fatigue and sleep disturbances among patients with cancer (634).

To help young women with breast cancer and their partners deal with the effects of their diagnosis, a program called Oncofertility! Pyscho-Education and Couple Enrichment provided **stress coping and marital communication strategies** along with information about fertility preservation services. Couples who participated in the study had reduced posttraumatic stress symptoms, improved stress-coping behaviors, and better marital relationships (635).

Improving Mental Health

The psychological challenges faced by survivors of cancer necessitate approaches that improve the mental well-being of this population (see **Challenges Faced by Cancer Survivors**, p. 132). Psycho-oncology is an interdisciplinary subspeciality within the cancer care continuum that aims to address the physical, behavioral, emotional, and psychosocial distress that arises for cancer survivors and their caregivers. Experts who are trained in psycho-oncology apply a holistic approach to destigmatize and address behavioral and psychosocial distress that is often caused by a cancer diagnosis and treatments (see **Sidebar 45**, p. 139).

SIDEBAR 46

Coping with Posttraumatic Stress After a Cancer Diagnosis

Both quantitative and qualitative data demonstrate that most cancer survivors experience posttraumatic growth, which is described as the personal growth that comes from experiencing a stressful, traumatic event (634,638,639). Posttraumatic growth is not necessarily a consequence of a traumatic event and to experience posttraumatic growth, survivors need to cultivate these feelings through personal development (640). Posttraumatic growth is being more appreciated as an approach to improving a survivor's mental well-being and recovery. Components of posttraumatic growth include:

RELATING TO OTHERS

Survivors find that their cancer diagnosis helped them prioritize and improve relationships and build stronger connections with those who are important to them. These experiences are attributed to increased willingness to express feelings, understand complex emotions, and better empathize with those struggling with similar challenges.

NEW POSSIBILITIES

Often described as a completely new lifestyle after cancer diagnosis, survivors may reevaluate their career or life path and choose to spend more time with family and friends. Change of lifestyle can often lead to healthier behaviors such as smoking cessation, engaging in a healthy diet and exercising.

PERSONAL STRENGTH

Living with and beyond a cancer diagnosis presents survivors with an immense challenge. While enduring such a difficult time, survivors may experience a belief that if they are able to defeat cancer, they can possibly manage any future challenge. This can prompt positive attitudes during times of stress or anxiety.

NEW APPRECIATION OF LIFE

Reevaluation of what it means to be in good health leads many survivors to describe feelings of appreciation of good health, a second chance at life, appreciation of the beauty in the world, and gratitude for the small victories in life. Others report having the perspective of living in the moment.

SPIRITUAL CHANGES

Receiving a cancer diagnosis can lead to finding or strengthening of spiritual beliefs and a deepening of faith. Spiritual growth has also been shown to help survivors with their recovery and the ability to manage day-to-day challenges.

Adapted from (641).

With the increased use of telehealth in oncology care (see **Sidebar 29**, p. 75), researchers are studying the effectiveness of bringing psycho-oncology practices like cognitive behavioral therapy and mindfulness stress reduction, as well as other interventions to survivors at their homes. In one clinical trial, researchers developed a smartphone app for breast cancer survivors to help reduce anxiety surrounding cancer recurrence. The group who had access to the smartphone app saw reduced recurrence-related anxiety after eight weeks compared to those who did not have access to the app (636). These types of technologies offer effective ways to help bring psycho-oncology care to patients, especially because currently there are a limited number of psychotherapists available for the growing number of cancer survivors.

Researchers are also trying to understand how survivors of cancer experience posttraumatic growth, which describes positive life changes that can develop because of traumatic and stressful events, such as a diagnosis of cancer (see **Sidebar 46**, p. 140). Posttraumatic growth may lead to perceptions of new possibilities, closer relationships with family and friends, development of personal strength, spiritual development, and a greater appreciation for life (637). Although the concept of posttraumatic growth is not new, its potential is just beginning to be appreciated within the cancer care community. The most influential factors that affect posttraumatic growth include the level of social support and the use of various coping strategies among survivors of cancer.

SIDEBAR 47

Patient Navigation

The first patient navigation program in the United States was designed specifically to address racial disparities in breast cancer screening and follow-up for Black women. Implementation of this program led to a 70 percent increase in 5-year survival in this group (644). While patient navigation is being increasingly recognized as a potent resource for helping cancer survivors, challenges in implementation remain.

BENEFITS

Patient navigation bridges a variety of gaps and addresses diverse needs across the cancer care continuum:

- Patient navigation improves access to screening, patient care coordination, symptom management, and follow-up care (642,645,646).
- Patient navigation reduces the cost of health care by reducing emergency room visits and missed appointments (643,647,648).

WHAT HAS BEEN DONE?

Recognizing the benefit of patient navigators, legislative efforts have been made to increase access to patient navigation, including:

- **The Patient Navigation Outreach and Chronic Disease Prevention Act** in 2005 which provided $25 million over 5 years to develop patient navigator programs and determine if they help reduce barriers to access to care and improve health care outcomes in underserved patient populations. This act was the first of its kind in the United States
- **The Patient Protection and Affordable Care Act** in 2010 which helped increase access to patient navigation programs for cancer patients and survivors.

Additionally, the American College of Surgeons' Commission on Cancer requires all accredited organizations to have a patient navigation program. The Community Preventive Services Task Force (CPSTF) also recommends the use of patient navigation services to increase cancer screenings among historically disadvantaged racial and ethnic populations and people with lower incomes.

CHALLENGES

Despite the benefits of patient navigators, challenges remain:

- There is often high variability in the organization and training of patient navigators in the United States. Lack of standardization can lead to different experiences for survivors.
- There is often confusion about coverage and financial benefits of patient navigator services through Medicare, Medicaid, and private/commercial insurers.

Delivering Care to Cancer Survivors

Coordinating Care

The multifaced approach to treating cancer necessitates providing survivors with appropriate care to address their many needs including transitioning from active treatment, coordinating follow-up appointments, addressing financial needs, and gaining access to other survivorship resources. While these resources are often available, understanding how or where to gain access to them can be challenging. Coordination of care is critically important to help patients identify and gain access to such resources.

Coordinating cancer care is most effective when a designated individual or a team of people helps a cancer patient or survivor to gain access to the resources they need. A systemic review of over 30 years of studies found that coordination approaches led to improvements among 81 percent of survivors across multiple facets of cancer care, including screening, patient experience, and quality of end-of-life care (642).

Patient navigators and clinical care coordinators are individuals who help cancer patients and survivors access resources more effectively (see **Sidebar 47**, p. 141). Furthermore, patient advocates, who are often cancer survivors themselves, are uniquely positioned to bridge critical gaps between patients, survivors, and the health care system.

Financial navigators can help reduce financial toxicity among survivors and their caregivers. These navigators can screen patients to determine if they are at an increased risk of financial toxicity and can provide assistance and resources. One study that implemented

financial navigators for patients with hematologic cancer and their caregivers found that the program secured an average of $2,500 in financial benefits for each participant (643).

Patient reported outcomes (PROs), which are reports given by patients on their status that have not been interpreted by a clinician or anyone else, are being used in connection with the patient experience, particularly among those participating in clinical trials (see **Sidebar 48**, p. 142). Incorporating the patient's perspective to understand treatment tolerability and efficacy is increasingly implemented in clinical trials and will improve the cancer treatment experience for patients in the real world (649). PROs are collected through questionnaires, which alert clinicians to the status of the patient regarding health-related quality of life, symptoms, and health-related behaviors (e.g., smoking, diet, physical activity) (650). Patients engaged in monitoring their symptoms may have improved clinical outcomes and reduced risk of emergency room and hospital visits compared to those who do not complete these questionnaires (651,652). Integration of real-world electronic health records with PRO assessments that provide automated alerts to clinicians will help improve patient outcomes.

Technologies that improve access to care, such as telemedicine (see **Sidebar 29**, p. 75) and smartphone apps, have become essential tools used by physicians, care teams, and patients. Increasingly, phone apps are being utilized by health care systems to assist with oncology support, treatment adherence, and follow-up care. Clinical trials of these apps are ongoing; however, preliminary evidence shows that they are utilized by patients and help improve the survivorship experience during and after treatment (653-655).

SIDEBAR 48

Patient Reported Outcomes

Patient Reported Outcomes (PROs) are a way for a patient to report changes in quality of life or functional status associated with health care or treatment. Patient-reported outcome measures (PROMs) are the tools used to measure PROs.

- PROs are **not interpreted by a physician** or anyone else and are a direct reflection of a patient's experience.
- PROs **can include health-related quality of life, functional status, symptom and symptom burden, personal experience of care,** and **other health conditions** such as anxiety and depression.
- PROs are **used in clinical trials** to reflect how a new drug may impact the patient, which can help inform how well or badly the drug is being tolerated.
- PROs are **being increasingly used by pharmaceutical companies** in the development of new therapeutics, which has the potential to improve the patient experience and increase safety by placing the patients at the center of decision-making.

Adapted from (650).

Supporting Caregivers

Caregivers comprise family members or friends who help patients with long-term chronic illness and manage any and all aspects of their care. One in five U.S. adults (ages 18 to 64), accounting for over 53 million people, provided care for another person in 2020, a significant increase from 43.5 million in 2015 (656). It is further estimated that four million of these caregivers are caring for an adult cancer patient. More evidence of the challenges faced by caregivers is becoming clear, and there are many opportunities to assist this vulnerable population.

Survivors require many resources that are often provided by their caregivers including arranging transportation, helping with day-to-day activities such as doctor visits, providing medical care or other clinical tasks, coordinating care, and giving emotional support. This often leads to caregivers deferring their own health care. One report shows that caregivers who are actively taking care of a family member were less likely to seek medical care including physician and emergency room visits (657). This is especially concerning among Black and Hispanic caregivers who spend more time caregiving compared to their White counterparts, potentially exacerbating health care disparities in these communities (658).

While patients with cancer are susceptible to adverse mental health events, their caregivers may also experience higher levels of mental illness compared to the general population (662). It is vital that evidence-based resources be made available to help improve services and ensure optimal health for cancer caregivers.

The use of smartphone apps specifically for caregivers to help manage their loved ones' care is being tested and utilized by hospital systems. For instance, apps that allow a caregiver to report symptoms and subsequently provide resources for self and patient care can help reduce burden and relieve anxiety experienced by the caregiver (659,660). While these apps have been utilized for many other chronic conditions, their increasing use and effectiveness among caregivers of cancer patients and survivors will need to be continually evaluated (661).

Envisioning the Future of Cancer Science and Medicine

IN THIS SECTION, YOU WILL LEARN:

- Innovative technologies are enabling a deeper understanding of cancer at a single cell and single molecule level.
- Artificial intelligence is poised to revolutionize cancer research and patient care.
- Wearable technologies have immense potential to improve health outcomes for patients with cancer.
- In-depth understanding of cancer biology is fueling progress in treating intractable cancers, such as glioblastoma multiforme and pancreatic cancer.
- Modulating the human microbiome is the next frontier in cancer therapeutics.

Unprecedented breakthroughs in cancer science and medicine, some of which are covered in this report, have accelerated the pace of progress against cancer. Thanks to decades of research-fueled fundamental discoveries and clinical advances, cancer mortality rates have decreased by 33 percent in the past three decades, and more cancer survivors are living fuller and longer lives.

Cancer researchers, including the **AACR president, 2023-2024, Philip D. Greenberg, MD, FAACR**, p. 144, are confident that this progress will continue to advance the frontiers of cancer science and medicine for the benefit of patients with cancer. Researchers across the nation's cancer centers are also extremely hopeful that the newly established AACR Cancer Centers Alliance will serve as a catalyst to fostering innovative and synergistic collaborations that address the many hurdles currently facing the nation's cancer centers and accelerate transformative lifesaving scientific discoveries for patients with cancer.

Revolutionizing Cancer Science and Medicine

These are exciting times as technological innovations continue to advance the frontiers of cancer science and medicine and accelerate the pace of progress against cancer. Within just two decades of the publication of the human genome, researchers have devised revolutionary new ways to study cancer in real time at single cell and single molecule levels. Knowledge gleaned from these in-depth observations is providing exciting new opportunities to detect, treat, and manage cancer. This section highlights some of the breakthrough technological advances that are moving the field of cancer science and medicine into a new era of progress against cancer.

New Frontiers in Cancer Research

Discovery science has played a pivotal role in progress against cancer, as documented in this and the prior 12 editions of the annual AACR Cancer Progress Report. Researchers are continually working to devise new ways to study unresolved mysteries of cancer, some of which are described below.

Spatial transcriptomics, or the study of transcriptomes (see **RNA Variations**, p. 31) at the single cell level in intact tissue, allows researchers to examine how cancer cells change during the course of cancer progression (663). While studying the transcriptome of a single cell is not a new approach (664), spatial transcriptomics takes this approach to the next level because it helps examine cells in the tumor or normal tissue where they are naturally located, thus minimizing any molecular changes that may occur during the process of isolating cells from a tumor or normal tissue. In recent years, researchers have employed spatial transcriptomics to answer some of the most elusive questions in cancer research, such as characterizing treatment responses (665), tracking tumor evolution (666), mapping and targeting the tumor microenvironment (667), and delineating tumor heterogeneity (668).

continued on page 146

Envisaging the Future of Cancer Research and Patient Care

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The progress in cancer research has been breathtaking, as has been documented in the *AACR Cancer Progress Report 2023*, and the 12 prior editions. When I started in the field of cancer medicine, cancers were treated with a sledgehammer approach, where chemotherapy and radiation therapy with limited selectivity for cancer cells were used. That has evolved remarkably in the last two decades into an era of precision oncology where individual patients are treated based on the characteristics of their own cancer. This evolution of cancer science and medicine in large part has taken place in four research areas.

The first area is cancer genomics and epigenomics. The revolution in this area was enabled at the turn of the millennium by advances in nucleic acid sequencing technologies and the mapping of the human genome. The latter was largely funded by NIH, and without such support, we wouldn't be where we are now with respect to our understanding of cancer at a cellular and molecular level. We can now readily and rapidly sequence a patient's cancer cells and understand precisely how they are different from normal cells. This helps identify specific abnormalities that can be targeted and that are selective for that patient's tumor.

The second area is synthetic chemistry, which has changed the way we target abnormalities in a tumor. Using synthetic chemistry, we can create and then modify large numbers of compounds and make them increasingly selective against cancer cells. Thus, synthetic chemistry is transforming the way we can design molecularly targeted therapeutics.

The third area, and focus of my own research, is immunotherapy. We've gone from skepticism about the role of the immune system in defending against cancer to the discovery of immune checkpoint blockade to the development and approval of many immune checkpoint inhibitors that are already helping patients with cancer live longer and fuller lives. The exciting new areas include the ability to engineer immune cells to target cancer precisely using adoptive cell therapy and the ability to produce therapeutic vaccines that will induce immune responses specifically against cancer.

The fourth area is computational biology, data science, and artificial intelligence, all of which are changing the ways we analyze and interpret data and use that information to drive new discoveries.

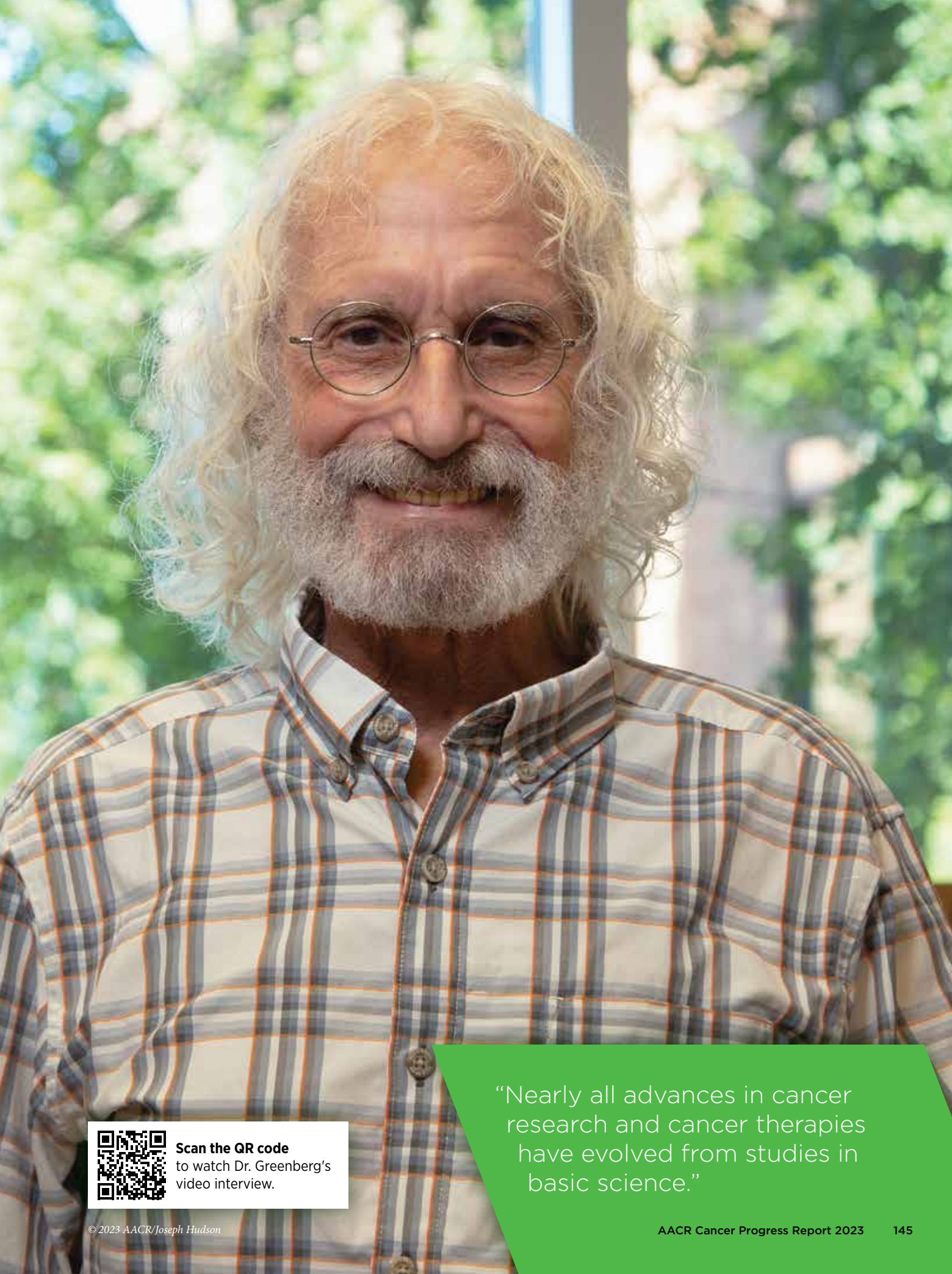
As we envision and advance the frontiers of cancer science and medicine, the idea of bringing two proteins together that normally don't interact, and making their interaction change the biology of the cell in a way that can be used for developing new anticancer therapeutics, is rapidly evolving. Advances in single cell technologies—which enable analysis of specific cell populations in a tumor to identify which genes are active in individual cells—are providing the basis for strategies that can target tumors more effectively. Similarly, liquid biopsy is another remarkably sensitive technology that has the potential to change the future landscape of cancer medicine, and I believe it will play an enormous role in the future in cancer prevention and early detection. These advances are moving rapidly from the laboratory to the clinic, and they're going to change the way cancer is prevented, detected, treated, and monitored, so we can continue to improve the quality of life for more patients with cancer.

Despite the progress we have made against cancer, it is important to recognize that much work still needs to be done in key areas. There is an enormous problem of disparities in access to health care and delivery of health care that disproportionately affects socioeconomically disadvantaged groups. Addressing these disparities would greatly decrease the number of cancer deaths in the U.S. Another challenge is the low participation of patients with cancer in clinical trials. Only about 6 percent of patients with cancer enroll in clinical trials for treatment. We need to communicate better the benefits of participating in clinical trials if we are to deliver on the potential of new therapeutics.

Nearly all advances in cancer research and cancer therapies have evolved from studies in basic science. The report provides enormous optimism and communicates to the public and policymakers the advances that have been delivered to patients with cancer and how they are transforming patients' lives. It also offers an insight into the problems that we are in the process of addressing.

We are in a time of unparalleled opportunities in cancer research. Not increasing investment in cancer research will impede the momentum against cancer. A substantial decrease in dollars for research that is on the table at Congress right now will also result in the loss of an incredibly talented and creative young workforce that is infusing new ideas and new technologies in cancer research. The perception that we can cut back on funding for cancer research without much impact is unrealistic and unacceptable.

There is no reason why cancer death rates can't continue to decline. But it will take commitment by cancer researchers, the government and the cancer community to invest in cancer research, and to increase patients' involvement in cancer trials. These strategies will improve the quality and survival of patients with cancer and realize the President's Cancer Moonshot goal of ending cancer as we know it.



Scan the QR code to watch Dr. Greenberg's video interview.

"Nearly all advances in cancer research and cancer therapies have evolved from studies in basic science."

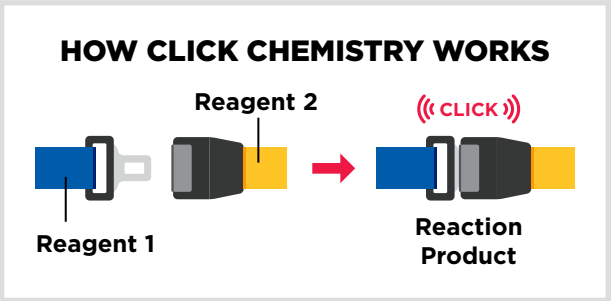
Extrachromosomal DNA (ecDNA) is large, circular, highly amplified pieces of DNA that have untethered themselves from chromosomes. ecDNAs are not found in normal tissues, and they are commonly detected in many of the most aggressive forms of cancer among children and adults (669), including during the transition from precancerous condition to cancer (670). Extrachromosomal DNAs are enriched for cancer-promoting oncogenes that drive tumor formation and growth, as well as gene regulatory elements that control their expression (671). Extrachromosomal DNAs can also contain genes, the products of which may help tumors escape immunotherapies (670).

Because ecDNAs do not follow the normal rules of chromosomal inheritance and are randomly inherited by daughter cells during cell division, much like bacteria, ecDNA enables tumor cells to change quickly, potently contributing to tumor heterogeneity, high oncogene copy number, and rapid treatment resistance (672), and resulting in shorter survival for patients (669).

Extrachromosomal DNA was first discovered in the 1960s, but was thought to be rare and of unclear importance. The application of powerful basic science technologies, DNA sequencing, and computational tools has revealed that ecDNA is very common among many of the most aggressive forms of cancer, contributing to poor outcomes for patients (669,673-677). The first ecDNA-directed anticancer therapy is now in clinical trials (678).

The 2022 Nobel Prize in Chemistry was awarded to K. Barry Sharpless, PhD, Morten Meldal, PhD, and Carolyn Bertozzi, PhD, for their pioneering roles in the discovery of click chemistry. Click chemistry refers to a class of simple chemical reactions that permit the joining of two molecules together. In medical research, click chemistry allows researchers to attach a chemical, such as a fluorescent probe that can be visualized by imaging, to a molecule or a protein present on or inside cells (679). Click chemistry is poised to revolutionize drug discovery and treatment of diseases, including cancer (680). As one example, researchers used click chemistry to specifically remove a type of sugar molecule commonly present on the surface of cancer cells, which resulted in enhanced antitumor immune response and improved effectiveness of immunotherapy (681).

The approaches highlighted here are fueling our ever-expanding knowledge of cancer initiation and progression and are providing new and better ways to understand and treat cancer.



The success of mRNA-based vaccines in controlling the COVID-19 pandemic has resulted in renewed interest in developing therapeutic (see **A New Era of mRNA-based Cancer Vaccines**, p. 128) and preventive vaccines for use in clinical cancer care. For example, researchers are investigating the potential of vaccines in preventing cancers in individuals who are diagnosed with inherited cancer syndromes, such as Lynch syndrome (see **Figure 5**, p. 31).

As genetic testing becomes more common and more people get tested for hereditary cancer syndromes, researchers estimate that one in every 288 people may be diagnosed with Lynch syndrome. These findings underscore the need to develop vaccines that can prevent cancer initiation and progression in individuals with hereditary cancer syndromes. Thanks to research, a new clinical trial is investigating a vaccine that will offer an effective, safe, and easy method of preventing Lynch syndrome-related cancers (682). Success of this study will lead to a new frontier in cancer prevention where preventive vaccines will play a pivotal role in reducing cancer burden.

Artificial Intelligence

Artificial intelligence (AI) is the ability of a computer to perform tasks commonly associated with human intelligence, such as how to act, reason, and learn. The use of AI in aiding health care professionals for early detection of cancer has shown tremendous potential, and several AI-assisted software and medical devices have already been approved by FDA for use in the clinic (see **Realizing the Potential of Artificial Intelligence for Early Detection of Cancers**, p. 65). Ongoing research, some of which is highlighted below, is exploring the potential of AI in other aspects of cancer research and patient care (683).

One exciting use of AI-assisted software is to extract existing knowledge from different sources of information—genomic data, test results, health care professionals' notes during clinic visits, patient reported outcomes, data from wearables, and scientific publications related to a patient's cancer—and present a complete view of a patient's health to clinicians. As one example, researchers used available clinical information from 1,348 patients with early-stage lung cancer to develop an AI-assisted model which accurately identified patients who were at low or high risk of cancer recurrence (684). Another machine learning model analyzed images and genomic datasets from 14 different types of cancer and discovered features that could accurately predict poor or favorable health outcomes (685).

Another way AI is helping to accelerate the pace of progress against cancer is by uncovering previously unknown aspects of cancer cells. For example, a deep learning model revealed that mitochondria—the powerhouses of cells—are organized differently in lung tumors with high metabolism (more aggressive), compared to those with low metabolism (less aggressive) (686). Researchers can use this new information in a number of ways.

For example, a new imaging technique that examines the location of mitochondria in lung cancer can be developed to distinguish highly aggressive tumors from less aggressive tumors.

An emerging strategy in early cancer detection is to screen for multiple cancers simultaneously (see **Moving Toward Minimally Invasive Cancer Screening**, p. 65). However, such tests generate a wealth of information, and a limitation so far has been the accurate and timely analysis of results from these tests. AI-based approaches have immense potential of overcoming this limitation. Artificial intelligence is also contributing to other aspects of cancer science and medicine. Researchers are already leveraging AI-based analyses of large genomic datasets in classifying tumors at a molecular level (687), determining tumor heterogeneity (688), diagnosing primary and metastatic cancers (689), identifying biomarkers for treatment selection (690), and predicting overall survival (691), among other applications across the cancer care continuum (692).

Another exciting application of AI in cancer medicine is its potential to create models that can predict how patients will respond to a treatment. In a recent study, researchers used clinical and genomic data from 700 patients with cancer, who were treated with ICIs, to develop a prediction model based on machine learning—a type of AI that is programmed to learn over time from the data provided to make predictions or decisions (693). The model accurately predicted how patients with melanoma, gastric cancer, and bladder cancer would have responded to the ICI treatment. Furthermore, the model's predictions were more accurate compared to those based on biomarkers currently being used in the clinic to predict a patient's response to the ICI treatment (693).

Cancer science and medicine are on the verge of an AI-driven revolution. However, it is important to be cognizant of the fact that AI-assisted approaches can introduce unintended biases in analyses and can further widen inequities in the burden of cancer experienced by medically underserved populations (694) (see **Sidebar 24**, p. 66). It is vital that the datasets used to train AI-based models accurately and proportionally represent population groups affected by the type of cancer being studied.

Wearable Technologies

Wearable technology, also called wearables, is a category of electronic devices that can be worn as accessories, embedded in clothing, implanted in the user's body, or affixed on the skin. Wearables are hands-free microcomputers with the ability to send and receive data via the Internet as well as to perform a variety of functions, such as counting steps or monitoring heart rate.

An exciting area of cancer research is the use of wearables that can be implanted on or inside the patient's body for delivering drugs effectively and automatically (695,696). Patients with cancer, especially elderly patients, often have to take many medications. According to one study of patients with cancer ages 70 years or older, 61 percent of the study's participants were taking five or more medications a day (697). Many of the anticancer therapeutics are pills taken orally, which can cause distress and inconvenience for patients, resulting in patients not taking their medication on time or at all (698), thus increasing the risk of adverse health outcomes (697).

Researchers recently reported the development of a wearable that can be attached to skin for delivering anticancer drugs (699). The study showed that the wearable successfully delivered anticancer drugs in a preclinical mouse model of melanoma and prevented recurrence of cancer. Importantly, there was no noticeable effect of the delivered drugs on other organs in the body (699).

Another focus of ongoing research is examining the potential of wearables to diagnose cancer. Recently, researchers reported the development of a flexible patch containing a miniaturized ultrasound scanner. The patch can be attached to a bra, which when worn scans the breast tissue. The ability to attach the patch in six different positions on the bra allows the entire breast to be imaged (700). Although the patch needs to be tested in a large number of individuals, such innovative applications of wearables are opening exciting new frontiers in cancer science and medicine.

Smart watches and health and fitness (activity) trackers are among the most commonly used wearables. According to a 2020 report, one in five U.S. adults regularly wears a smart watch or a fitness tracker, and more than half of those who do support sharing of data from these devices with their health care providers and with researchers (701).

Researchers are testing the potential use of smart watches and activity trackers in clinical cancer care in several ways (702). Findings from a number of studies have shown that use of wearables among cancer patients and survivors helps encourage physical activity (703); predict whether patients receiving active cancer treatment are at an increased risk of hospitalization (704); identify patients who are fit for certain types of cancer treatments (705); examine association of sleep patterns with overall survival (706); and determine quality of life (707). Future studies with large numbers of patients will further strengthen the utility of wearables in cancer science and medicine as an exciting new frontier that can measure biometric parameters in patients and deliver care remotely (708), thus harnessing technological advances to further expand and improve telemedicine.

Tackling Difficult-to-Treat Cancers

The consistently declining rates of U.S. cancer deaths in recent years underscore the unprecedented progress against cancer

(see **Cancer in 2023**, p. 12). However, treatment options for certain types of cancer, such as cancers of pancreas, and those that originate in the nervous system, remain limited. Thanks to rapid advances in our understanding of how cancer develops (see **Understanding the Path to Cancer Development**, p. 24), researchers are taking innovative approaches to tackling difficult-to-treat cancers. Here we present an overview of some of the most promising breakthroughs in treating two types of cancer—glioblastoma and pancreatic cancer—as examples of progress against currently intractable cancers.

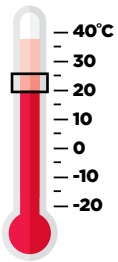
Glioblastoma

Glioblastoma—the most common and deadly type of brain cancer—is highly resistant to chemotherapy, and surgery and/or radiotherapy are ineffective. No new drugs have been approved for glioblastoma over the past decade, and only 6.9 percent of patients survive five years after being diagnosed with glioblastoma (29), underscoring an urgent need to find better treatments for the disease.

An active area of scientific discovery is understanding the relationship between resistance to treatment and how the tumor utilizes nutrients. Two recent studies found that certain types of gliomas, a larger category of cancers of the nervous system that includes glioblastoma, produce large quantities of chemicals, called pyrimidine nucleotides, which are the building blocks of DNA. Findings of the studies show that gliomas become dependent on these chemicals for survival, and when the production of pyrimidine nucleotides is blocked with a drug, tumors shrink in animal models of glioma (709,710). Researchers are now planning clinical trials to test the drug in people with gliomas.

One of the challenges in effectively treating glioblastoma (and other cancers that originate in the brain) is delivering drugs to the brain, which is naturally protected from pathogens and other toxins by a thin layer of tissue and blood vessels, called the blood–brain barrier. Even the most potent chemotherapy drugs cannot cross this barrier. Researchers are testing novel approaches to increase the concentration of drugs in the brains of patients with glioblastoma. In a phase I clinical trial, an ultrasound device was implanted in the brains of 17 patients who had recurrent glioblastoma (711). When activated, the device repeatedly, but temporarily, opened the blood–brain barrier, increasing the concentration of a chemotherapy drug by sixfold in patients' brains without causing any serious side effects (711). The study is now in phase II of clinical development.

In a recent study, researchers found that **lowering temperature around the tumor** to 20˚C to 25˚C using an implantable device **doubled the median survival** in two preclinical animal **models of glioblastoma** (712).



SELECTED IMMUNOTHERAPEUTICS CURRENTLY IN CLINICAL DEVELOPMENT TO TREAT GLIOBLASTOMA

Type of Immuno-therapeutic	Target	Clinical Trial Phase
CAR-T cells	IL13 receptor	I
	EGFRvIII	I/II
	B7-H3	I/II
CAR-NK cells	HER2	I
Immune checkpoint inhibitors (ICIs)	PD-1/PD-L1	III
	PD-1/PD-L1 & CTLA-4	II
	PD-1/PD-L1 & LAG-3	I
Oncolytic viruses	–	I/II
Vaccines	EGFRvIII	II/III
	IDH1	I
	DCVax-L	III

Developed from (713).

Clinical advances and breakthroughs in immunotherapy for other tumors (see **Immunotherapy: Pushing the Frontier of Cancer Medicine**, p. 99) have inspired treatment of glioblastoma with immunotherapeutics. Different classes of immunotherapeutics are at various stages of clinical development to treat glioblastoma (713). There are several ongoing CAR T-cell candidates for glioblastoma treatment, including CARs directed against proteins, such as EGFRvIII, IL13Rα2, and B7-H3, that are abundantly present on the surface of glioblastoma cells (714). In addition, CAR-NK cells are being evaluated in clinical studies of glioblastoma against different targets, such as HER2 (715).

Therapeutic vaccines have also shown promise in the treatment of glioblastoma. In a phase III clinical trial, researchers added a vaccine based on dendritic cells (see **Sidebar 38**, p. 100) to the standard of care treatment (716). Addition of vaccine more than doubled the overall survival in patients who were newly diagnosed with glioblastoma or who had recurrence of the disease at 60 and 30 months, respectively (716). These results demonstrate a remarkable

In the United States between 2001 and 2018, **the incidence of pancreatic cancer** more than doubled in younger women **ages 15 to 34,** compared to men of the same age range (38).

advance and underscore the promise of immunotherapy in treating currently intractable cancers.

Pancreatic Cancer

According to U.S. estimates for the year 2023, 64,050 new cases of pancreatic cancer will be diagnosed and 50,550 people will die from the disease (28). Pancreatic cancer is a highly aggressive disease, with a 12 percent 5-year survival rate, and treatment options primarily limited to surgery, radiation therapy, and chemotherapy.

Researchers are actively working to uncover novel ways to improve health outcomes for patients with pancreatic cancer. One of the ways to tackle this disease is to identify risk factors that can contribute to the development of pancreatic cancer. For example, a new diagnosis of diabetes, sometimes also called new-onset diabetes, is a known risk factor for developing pancreatic cancer, although the reasons are not clear (717). Another active area of research is to develop safe and reliable methods of detecting pancreatic cancer early. Currently, USPSTF does not recommend screening for pancreatic cancer in individuals who do not have any symptoms of the disease (718). Ongoing studies are focused on developing prediction models and genetic tests to detect pancreatic cancer in individuals who are at high risk of developing the disease (719).

ONGOING NCI INITIATIVES TO DEVELOP TESTS FOR EARLY DETECTION OF PANCREATIC CANCER

- **New Onset-Diabetes (NOD) Study** aims to develop a blood test that can identify individuals with a new diabetes diagnosis who may need further testing for pancreatic cancer (720).
- **The Pancreatic Cancer Detection Consortium (PCDC)** aims to develop a blood test that can identify early pancreatic cancer in average-risk individuals. Researchers in PCDC are also working to improve imaging of the pancreas by developing methods that can pick up small deposits of tumor cells (721).

In a preclinical study in an animal model of pancreatic cancer, **combining two groups of immunotherapy drugs**—one that activates the cancer-fighting T cells to move into the tumor and the other two that release the "brakes" from T cells and unleash them against cancer cells—**significantly reduced tumor size in about half of the mice and the tumor disappeared completely in 25 percent of the mice** (725).

Recent studies have also unveiled potential new drug targets for the treatment of pancreatic cancer. For example, one study found that pancreatic cancer meets its nutrient needs by using a metabolic pathway that is predominantly active in infants and is rarely used by normal cells in adults (722). When researchers blocked the pathway in preclinical animal models of pancreatic cancer with a therapeutic that blocks the metabolic pathway, tumor growth was severely inhibited (722). In another preclinical study, researchers found that pancreatic cancer cells use a different type of fuel, called uridine, when they do not have access to sugar, the most common type of fuel used by cells in the human body. Starving pancreatic tumors of uridine stopped tumors from growing (723).

A recent scientific discovery revealed that pancreatic cancer cells make an abnormal form of a protein called collagen. Collagen is a protein in the extracellular space which provides structure to tissues and is found almost everywhere in the human body (724). The abnormal collagen produced by pancreatic cancer cells promotes tumor growth. When its production or function was blocked using a therapeutic in a preclinical animal model, cancer-fighting immune cells started to move into the tumors, and tumors shrank dramatically in response to a commonly used immunotherapy drug, which was otherwise not very effective in the presence of abnormal collagen (724).

Findings of these preclinical studies are encouraging and pave the way to develop novel and effective treatment options for patients with pancreatic cancer in the near future.

An in-depth understanding of the genetic makeup of pancreatic cancer has identified mutations in several genes, such as *KRAS*, that contribute to pancreatic cancer development (726). One KRAS mutation, called G12D, is the most common in pancreatic cancer and is present in about 35 percent of patients with pancreatic cancer.

FIGURE 21

The Gut Microbiome: A New Frontier in Cancer Prevention, Early Detection, and Treatment

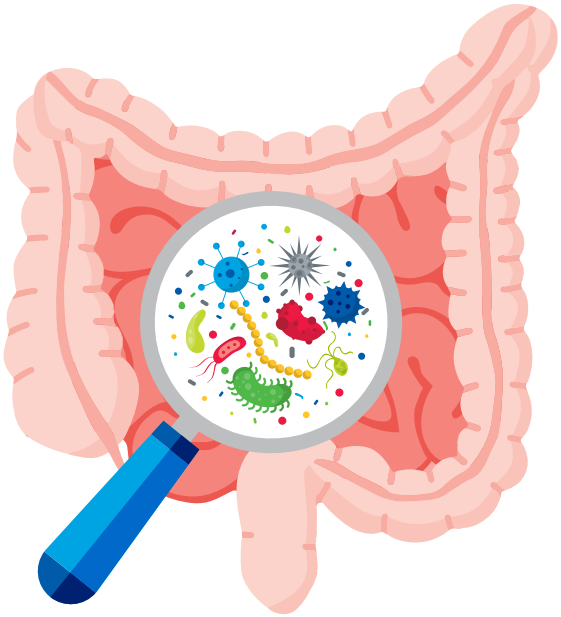
Prevention
Modifying microbiome through diet or medication

Early detection
Microbiome analysis to identify biomarkers

Drug discovery
Microbiome-derived compounds or microbiome-targeted drugs as cancer therapeutics

Therapy optimization
Modifying microbiome to augment responses to treatment

Precision medicine
Microbiome analysis to create patient's personal profile



The gut microbiome is an exciting new area in cancer research. Investigations are underway to study whether it is possible to harness the human gut microbiome to prevent, detect, diagnose, or optimize cancer treatment. Manipulating the microbiome through lifestyle modifications such as changes in diet, might aid in reducing the risk of developing cancer by suppressing chronic inflammation, while detection of certain microbial species that are frequently associated with cancer incidence may help in the early detection or diagnosis of disease. The gut microbiome may also have a dramatic impact on the efficacy of anticancer immunotherapies and chemotherapies. Modulating the microbiome in patients with cancer through advanced probiotics, fecal transplantation, or pharmacologic interventions may open up new opportunities to improve patient outcomes and further precision medicine.

Adapted from (489).

In recent years, there have been exciting new advances in targeting the KRAS G12D mutation. As one example, a recent study showed that a molecularly targeted therapeutic directed against the mutation shrank tumors or stopped their growth in preclinical animal models of pancreatic cancer (727). Notably, the drug also allowed the cancer-fighting immune cells to enter the tumor microenvironment. Researchers are now planning to combine this drug with an immunotherapeutic to evaluate whether the combination will be even more effective against pancreatic cancer.

In a phase I/II clinical trial, treatment with another KRAS targeted therapeutic, sotorasib, shrank tumors in about 20 percent of participants (728). Sotorasib, which has already been approved to treat patients with lung cancer, is directed against a different KRAS mutation called G12C (see **Figure 16**, p. 84), which is present in approximately 1 to 2 percent of patients with pancreatic cancer. Findings from these studies are encouraging and underscore the continued efforts to develop effective treatments against an intractable form of cancer.

Immunotherapy, especially adoptive cell therapy and vaccines, has shown great promise against pancreatic cancer. As of March 2022, multiple CAR T-cell therapies, targeting various proteins such as CD133, EGFR, HER2, and MSLN, were in clinical trials for treatment of pancreatic cancer (729). Together, these research efforts are ushering effective methods for early detection and treatment of pancreatic cancer into a new era, with immense potential of bringing hope to patients with this aggressive form of cancer.

Targeting the Microbiome in Cancer Treatment

The human microbiome is the collection of all microorganisms (e.g., bacteria and fungi) and viruses that live in the gut, skin, and mouth, among other parts of the body. Most

microorganisms that make up the human microbiome are helpful to our health, but a smaller number are potentially harmful. Accruing evidence suggests that the balance between helpful and potentially harmful microorganisms in the microbiome contributes to overall health, and an imbalance can contribute to a number of diseases, including cancer (730).

Composition of the human microbiome is affected by genetics as well as lifestyle factors, such as diet, environment, and antibiotic use (731). An imbalanced microbiome can cause inflammation in the intestine and contribute to colorectal cancer (732,733). There is mounting evidence that an imbalanced microbiome can also modulate tumor formation, metastasis, and resistance to treatment (734-736).

Research has shown that tumors also harbor microorganisms and the type of microorganism present in tumors can predict health outcomes (see **Figure 21**, p. 150) (737). For example, two recent studies, one examining 35 different types of cancer and the other investigating cancers of the lung and gastrointestinal tract, revealed that tumors have unique populations of fungi that can predict cancer-specific outcomes (738,739).

Several studies point to the link between microbial composition and response to cancer treatment (740). Researchers have found that modulating the microbiome can boost the effectiveness of anticancer treatment. As one example, oral administration of a type of bacteria that is naturally present in the microbiome enhanced the antitumor activity of a PD-1-targeting ICI (741). Conversely, findings from a retrospective study show that the overall survival of patients who were taking antibiotics that alter the microbiome's diversity prior to immunotherapy was negatively impacted (742). In another study, researchers found that patients with B-cell lymphoma who were not treated with antibiotics showed better clinical response to CAR T-cell therapy (743).

There are many ongoing clinical trials investigating the role of the microbiome in cancer therapy (740). Some are modulating the microbiome as a way to reduce or prevent toxic side effects of cancer treatment, while others are combining modulation of the gut microbiome with immunotherapy to enhance the effectiveness of the latter. Findings from these studies have the potential to revolutionize future cancer treatment and care.

Advancing the Future of Cancer Research and Patient Care Through the Adoption of Evidence-based Policies

IN THIS SECTION, YOU WILL LEARN:

- Continued investment in medical research through NIH and NCI is essential to making progress against all aspects of cancer, including prevention, early detection, treatment, and survivorship care.
- FDA's leadership and many innovative initiatives are ensuring that patients are receiving safe and effective treatments in an expedited time frame.
- Expanded insurance coverage for cancer screening and newly proposed standards to reduce tobacco-related illness are important steps to preventing cancer burden.
- Legislation that reauthorizes essential research and data collection programs is important to improve outcomes for children and adolescents diagnosed with cancer.

The National Institutes of Health (NIH) is the largest source for medical research funding in the United States and the world (744). Its goals are to promote innovative research, develop scientific resources, expand the knowledge base in science and medicine, and foster the highest levels of scientific integrity (745). Within NIH, approximately 1,200 Principal Investigators perform medical research including behavioral research with the goal of changing lives and advancing medical research. Additionally, NIH awarded 58,368 grants to outside organizations in fiscal year (FY) 2022 for projects that have the potential to transform medical research and deliver lifesaving medical breakthroughs (746).

The National Cancer Institute (NCI) plays a pivotal role in driving progress against cancer. NCI conducts and supports research, training, and other activities related to the prevention, diagnosis, and treatment of cancer, while furthering basic science to advance our knowledge on cancer-causing factors like cell growth and differentiation. Furthermore, NCI-designated cancer centers across the United States serve as a model for advancing research from the laboratory to the clinic and introducing cutting-edge discoveries to patients and the greater community.

Both NIH and NCI rely on robust, sustained, and predictable funding for medical research from Congress to carry out their missions. Support from key members, most specifically the Chair and Ranking member on the Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies in the House [Representatives Robert Aderholt (R-Alabama) and Rosa DeLauro (D-Connecticut), respectively] and Senate [Senators Tammy Baldwin (D-Wisconsin) and Shelley Moore Capito (R-West Virginia)], respectively,] is vital to ensuring predictable funding increases for medical research.

Another federal entity that shares NIH's commitment to advancing cancer research is the Advanced Research Projects Agency for Health (ARPA-H). Officially formed in March 2022, ARPA-H is the nation's newest medical research agency that functions as an independent entity within the organizational structure of NIH. Unlike other federal agencies involved with medical research, ARPA-H focuses on advancing high-potential, high-impact research that cannot be achieved through traditional research or commercial pathways. Cancer is one of three diseases the new research agency will initially prioritize, and in July 2023, ARPA-H launched a first-of-its-kind program to develop new technologies to help surgeons to remove tumors with greater precision and accuracy (747). While the future of ARPA-H holds potential, we are united in asking that its funding supplement, rather than supplant the core investments that are provided to NIH and NCI.

Additionally, the U.S. Food and Drug Administration (FDA) is a key federal agency in our nation's efforts against cancer. For example, the FDA Oncology Center for Excellence leverages the skills of regulatory scientists to support the approval of safe and

effective oncologic medical products. Additionally, as tobacco products, including electronic cigarettes, remain the leading preventable cause of cancer, recent FDA efforts through its Center for Tobacco Products seek to reduce the use of these products.

The Centers for Disease Control and Prevention (CDC) is another federal agency that plays an important role in driving progress against cancer. The agency's Division of Cancer Prevention and Control (DCPC) works with state, local, territorial, and tribal health entities to develop and implement effective cancer prevention and screening practices. Key CDC cancer initiatives include programs to support early detection of breast, cervical, and colorectal cancer, as well as support for central cancer registries that are vital to data collection on cancer.

The Biden administration remains committed to "ending cancer as we know it." In February 2022, the administration relaunched the Cancer Moonshot, a whole-of-government initiative that aims to reduce the cancer death rate in the U.S. by 50 percent by 2047 (748). To help achieve the goals of the Cancer Moonshot, the National Cancer Plan lays out eight goals to accelerate progress against cancer (309).

Funding support for medical research and the many cancer programs at NIH, NCI, FDA, and CDC remains critical, but the June 2023 agreement to raise the debt ceiling is making the prospect of increased appropriations for these agencies in FY 2024 very challenging. To ensure that federal agencies can advance progress against cancer, the medical research community must continue to advocate before Congress the importance of supporting robust, sustained, and predictable investments, most especially for the medical research supported by NIH.

Investments in Research Fuel a Healthier Future

Remarkable advances in medical research have led to significant improvements in cancer prevention and reductions in cancer mortality. Investments in cancer research have resulted in a 33 percent decrease in cancer deaths since 1991, preventing an estimated 3.8 million deaths. This progress is a result of NIH and NCI investments in research that developed state-of-the-art anticancer therapies and more effective screening tools to detect cancers at the earliest possible stage, as well as initiatives through FDA and CDC to raise public awareness of the importance of cancer prevention and cancer screenings. As a result of these efforts, there are now more than 18 million cancer survivors living in the United States (see **Supporting Cancer Patients and Survivors**, p. 132).

Continued federal investments are needed to further the progress against cancer. Beginning in FY 2005, a decade of stalled funding at NIH caused budgets to be eroded by inflation (see **Figure 22**, p. 154). As a result, NIH's purchasing power—the amount that each dollar invested can buy—was reduced by nearly 25 percent compared to the previous decade. This had a devastating impact on the ability of NIH to adequately fund research and meet the needs of the medical research community. The current political climate surrounding appropriations and NIH funding has once more created an uncertain environment for this necessary research.

The FY 2024 Presidential Budget Request includes $48.6 billion in discretionary and mandatory resources for NIH, an overall increase of $811 million from FY 2023 (749). Within this budget, $7.8 billion (an increase of $503 million) was proposed for NCI (750); $2.5 billion was requested for ARPA-H (an increase of $1 billion); and $716 million for the reauthorization of the Cancer Moonshot through FY 2026.

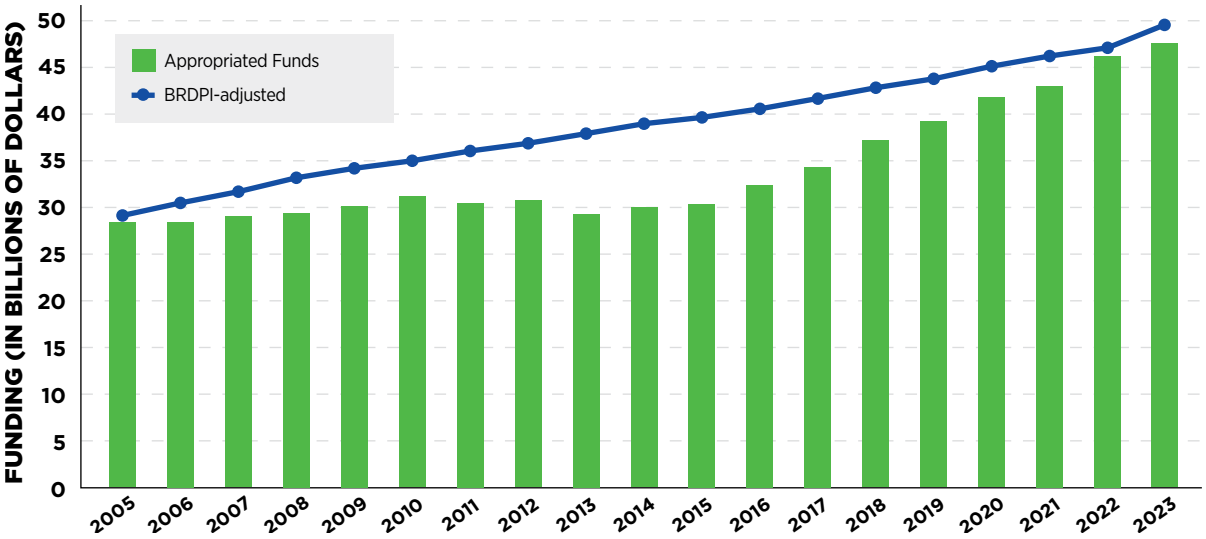
Major steps towards a cancer-free future for all can be achieved with these supplementary investments, as well as other FY 2024 allocations. A proposed $394.5 million investment is slated for CDC's Division of Cancer Prevention and Control (DCPC) programs. The National Comprehensive Cancer Control Program, including the Cancer Genomics program, intends to increase the number of individuals who are appropriately referred to genetic counseling and testing; the National Breast and Cervical Cancer Early Detection Programs to enhance breast and cervical cancer screening and diagnostic services for uninsured and underinsured American women, addressing inequity in cancer prevention efforts; and the Colorectal Cancer Control Program to increase colorectal cancer screening rates among people ages 45 to 75. The Division works with state and local governments, community organizations, and health care providers to promote cancer prevention and early detection. These collaborations include funding for central cancer registries; comprehensive cancer control, which includes state, tribal, local, and territorial organizations; the National Breast and Cervical Cancer Early Detection Program; and initiatives focused on colorectal, skin, prostate, and ovarian cancer, as well as HPV-associated cancers (751).

While Congress has made decisive commitments to medical research over the last eight fiscal years, a now strained budget is leading to a more uncertain future for medical research. Investments have been proposed to expand opportunities in medical research, cancer prevention, and cancer treatment. But the risk of not passing President Biden's FY 2024 Budget, which is already below the One Voice Against Cancer (OVAC) budget provided to Congress, threatens the future funding of NIH, NCI, and other institutions. The need for increased funding, as opposed to flat funding, comes directly from the NCI's budget projections, with their Professional Judgment Budget detailing the need for a $2.7 billion increase.

Flat funding can set a precedent for lower funding in the future because future budget requests will have to be built from the FY 2024's final budget. Additionally, if funding is kept at the same rate as FY 2023, it will not meet or address new costs

FIGURE 22

NIH Funding: Continuing the Momentum of Robust Increases



The National Institutes of Health (NIH) appropriations from 2005 to 2022 have steadily closed the gap between appropriated funds and projected costs to conduct research, as illustrated by Biomedical Research and Development Price Index (BRDPI), shown in blue. Continued bipartisan efforts are urgently needed to prevent stagnant funding and ensure a continued investment in lifesaving cancer research.

Source: (753).

brought on by inflation. The previous stagnant period for NCI funding prior to FY 2015 prevented the institute from keeping up with the then 3.7-3.8 percent biomedical inflation rate (752); the current biomedical inflation rate is 4.5 percent (753). Successfully funded applications dropped below 20 percent during this period (see **Figure 23**, p. 155), deterring young investigators from entering the field and decreasing America's competitive stance against other global biomedical research institutions. Keeping these applications funded is essential to combating cancer and spurring future discoveries (see **Research: Driving Progress Against Cancer**, p. 12).

With so many scientific opportunities available to make progress against cancer and other diseases, it is imperative that our elected leaders continue to provide robust, sustained, and predictable funding increases for medical research and cancer prevention at NIH, NCI, CDC, and FDA. The Senate Committee on Appropriations Chair Patty Murray (D-WA) and the Vice Chair Susan Collins (R-ME) remain steadfast in their bipartisan commitment to medical research, as do many members of the Senate. However, some House Republicans are demanding that federal budget cuts must go even deeper than what President Biden and Speaker Kevin McCarthy agreed to in the recent bipartisan debt limit compromise that limited overall federal spending for the next two fiscal years. This is creating a contentious budget environment in the House of Representatives that will further complicate efforts to secure a funding increase for NIH and NCI in FY 2024.

A Diverse Cancer Research and Care Workforce Drives Innovation

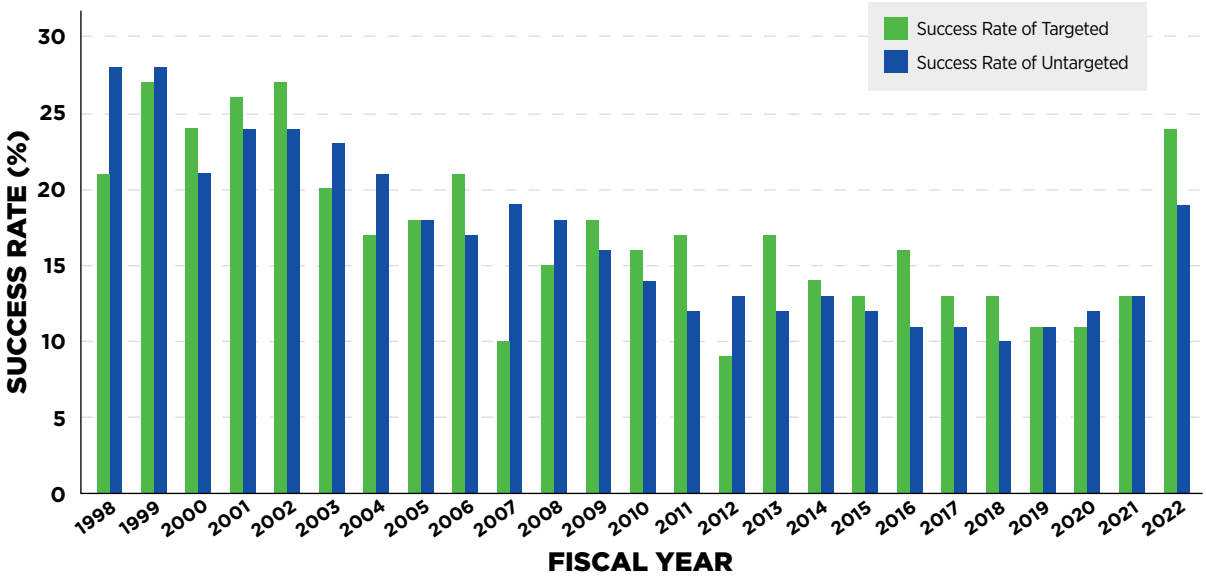
To realize the full potential of the medical research enterprise, research institutions must be proactive in recruiting, supporting, and retaining a cancer research and care workforce that reflects the diversity of our society. Collaborative and intentional efforts are needed to train and support the current and next generations of cancer researchers throughout their career paths to prevent and cure all cancers. Within the cancer research and care workforce, early-career researchers invigorate progress against cancers as they bring innovative ideas and new questions. NIH and NCI play an important role in fostering the career development of young researchers to become the scientific and clinical leaders of the future.

More specifically, NCI has taken steps to support early-stage, tenure-track research faculty. For example, NCI has created several programs and policies to help establish independent laboratories including:

- Setting a payline in the 17th percentile for "early-stage investigators" (researchers within 10 years of completing their terminal degree) (754);

FIGURE 23

NCI Success Rates



Success rates at the National Cancer Institute (NCI), i.e., the percentage of grant applications that receive funding through NCI, have steadily declined over the past two decades for both targeted and untargeted research. Targeted research is the research for which an institute solicits grant applications in a specific scientific area using Request for Applications (RFAs), and funds meritorious applications from a pool of dollar amount specifically set aside for that research area. Untargeted Research is the research that is not funded through grant solicitation in response to an RFA.

- Converting the most meritorious NCI R01 applications from early-stage investigators to Method to Extend Research in Time (MERIT) R37 awards (755), which provide longer term support; and

- Supporting the Cancer Moonshot Scholars program, which seeks to diversify the NCI R01 portfolio to increase the number of applications from early-stage investigators from diverse backgrounds, including those that are underrepresented in the STEM workforce (756).

The influx of innovative ideas from young scientists with various backgrounds is critical for future breakthroughs against cancer and other diseases.

It is concerning that there has been a decline in the number of postdoctoral researchers in the life sciences, as many have expressed that low compensation, diminishing funding sources, and uncertain career trajectories were key drivers of that dissatisfaction in extramural postdoctoral research training (757-759). To understand how to address the factors that influence postdoctoral training and retention in academia, NIH released a Request for Information (760) in February 2023 in order to receive feedback that will inform recommendations to better support the medical research community. As Congress considers both annual appropriations and supplemental funding, it will be vital to invest in additional resources to support early-career researchers. Robust, sustained, and predictable funding increases for NIH and NCI are critical to ensure that these programs continue.

Ensuring Safe and Effective Cancer Therapies Through Regulatory Science

FDA performs a critical role in ensuring that new anticancer therapies are safe and effective for patients. FDA's complexity and workload have continually increased as new categories of therapies become available and inspections are needed across the globe. Therefore, FDA's staff, technology, and processes must also be continually enhanced in order to provide effective and efficient oversight of drug development and manufacturing. FDA is funded through user fees paid by the pharmaceutical industry and congressionally appropriated funds, both of which are critical to support staff, technology modernization, and regulatory science programs that improve clinical trials. These crucial funds support FDA's mission to regulate approximately one fifth of the U.S. economy that includes ensuring medicinal products used by Americans are safe and effective.

FDA's Oncology Center of Excellence (OCE) was created in 2017 by the 21st Century Cures Act to provide dedicated staff to improve efficiency in oncology drug development and review. OCE facilitates collaborations between staff members with oncology expertise from other FDA centers, including the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation (CBER), and Center for Devices and Radiological Health (CDRH).

Diversifying and Decentralizing Trials

Clinical trial participation yields advances in treatment and survival for the types of cancers and groups of patients represented (761). Additionally, clinical trial participants frequently experience improved outcomes compared to nonparticipants (762), as they receive a greater level of care during clinical visits (763). While more than half of adult patients with cancer choose to enroll in trials if asked by their providers (764), clinical trial participation rates remain very low in the United States. Only 8 percent of adult patients and 19.9 percent of pediatric and adolescent patients with cancer participate in clinical trials (765,766). Academic medical centers experience greater than average trial participation rates (765), but most patients with cancer are treated at community clinics or hospitals where trials have not been historically available. Unfortunately, more than 75 percent of patients with cancer are ineligible for trials because there are no trials available for their specific disease or they are excluded because of strict eligibility criteria related to other health conditions (765). Additional challenges to enrollment in clinical trials include absence of health care facilities in some communities, lack of trust in medical research and institutions, family responsibilities, and costs and time related to participating (767-769). These factors contribute to a clinical trial population which does not represent the real-world population of patients who may use the new therapies. This discrepancy leaves open questions on safety and efficacy for people from groups that are not adequately represented in clinical trials, and particularly groups that bear disproportionately higher cancer incidence and death.

To improve representation in clinical trials, it will be critical that trial sponsors and researchers prospectively integrate diversity strategies with traditional drug development strategy. Historically, diversity has primarily been considered in hindsight, when it is too late to make meaningful changes to clinical trials underpinning regulatory submissions. Included in the federal appropriations omnibus for FY 2023 was a provision that allows FDA to require companies to develop a Diversity Action Plan for registrational trials as well as document their success at meeting diversity goals (770). The new law also allows FDA to require additional postmarketing clinical trials to follow-up on important signals for specific subgroups of patients identified during premarketing trials. In April 2022, OCE released draft guidance on creating prospective diversity action plans and is now working towards finalizing the guidance (771). In June 2023, AACR, FDA, and several industry partners collaborated on a special article that outlined steps clinical trial sponsors can take to improve diversity in clinical trials, thereby improving access to innovative cancer therapies for all patients (772). They called on the entire cancer research community to expand the number of clinical sites involved in research, broaden trial eligibility criteria, address barriers to participation, and continue ongoing conversations among broad stakeholders, including patients. Recommended changes to clinical trials to enhance diversity as well as other improvements are summarized in **Table 4**, p. 157.

In the wake of the COVID-19 pandemic, every clinical trial now includes some form of decentralized element, such as consenting patients remotely, using local laboratory test and imaging facilities, and telehealth visits for monitoring side effects. These approaches have greatly reduced the burden of trial participation for patients and health clinics alike. Decentralization also provides value to industry by enabling cost savings, increasing patient enrollments, simplifying trial designs, and promoting faster completion of trials. When the pandemic's public health emergency designation expired earlier this year, many in the cancer research community were concerned about a lapse in COVID-era guidance that enabled greater decentralization. In response, FDA issued guidance to continue supporting decentralized approaches (771). However, many of these decentralized elements were allowed prior to the COVID-19 pandemic and the limiting factors for widespread adoption revolve around implementation within industry and academic medical centers. As the use of decentralized elements grows, new data demonstrating the value of these changes will hopefully enhance further adoption.

Rapidly Delivering Safe and Effective Therapies to Patients

Waiting for definitive evidence of clinical benefit for new therapies before sponsors apply for FDA review can take many years. This delay can mean that patients with deadly diseases who could benefit may die before the drug becomes approved. In 1992, FDA created the Accelerated Approval pathway as a response to the devastating HIV pandemic (773). Accelerated Approvals leverage early outcome data that are suggestive of "clinical benefit," but not necessarily a direct measure of clinical benefit for serious diseases that have unmet medical needs. Between 2011 and 2020, 45.6 percent of new cancer drugs were approved through the Accelerated Approval pathway, and cancer therapies accounted for 80 percent of all Accelerated Approvals (774). For cancer therapies, progression-free survival, response rate, and side effect rates are early endpoints frequently considered for Accelerated Approval. However, Accelerated Approval also carries a requirement for companies to continue studying the therapy to demonstrate clinical benefit, most often improved overall survival.

In March 2023, FDA issued draft guidance on considerations for clinical trial designs to support enhanced Accelerated Approval

TABLE 4

Summary of Current Clinical Trial Practices and Recommended Changes

DRUG DEVELOPMENT TOPIC	CURRENT PRACTICES	RECOMMENDED PRACTICES
Trial Diversity	• Demographic data are analyzed after trials are completed	• Build long-term partnerships with patient and community organizations • Develop diversity strategies prospectively • Address barriers to participation • Support clinical research sites in historically underserved communities
Decentralized Trials	• Patients have frequent in-person visits to a large academic medical center	• Increase use of telehealth visits • Enable remote consenting • Utilize local health clinics and imaging • Minimize unnecessary data collection
Accelerated Approval	• Relies on single-arm trials • Confirmatory trials are initiated following Accelerated Approval	• Increase use of randomized trials • Either start confirmatory trial before submitting Accelerated Approval application, or continue existing trial
Dose Optimization	• Gradually increase dose until patients cannot tolerate the drug	• Identify doses that elicit the intended biological effects • Further study more than one dose following a dose-finding trial
Overall Survival Data	• Many trials do not collect or plan to analyze overall survival data • Patients are followed for standardized time frames	• Plan to collect and analyze overall survival data for every trial, even if it is exploratory • Justify length of follow-up based on data • For targeted therapies, prioritize recruitment of biomarker-positive patients

applications (775). A key focus of the guidance was encouraging trial sponsors to conduct more randomized controlled trials instead of the commonly used "single-arm" trials that lack control arms. While single-arm trials have been useful for developing new classes of drugs for diseases that previously had no effective treatment options, the clinical landscape has evolved (see **Figure 14**, p. 73). It is now more appropriate to compare new drugs against the current standard of care to ensure that novel treatments provide greater benefits or lower toxicities than what is currently available. The guidance also recommended that trial sponsors either continue and expand the trial used for Accelerated Approval or start a second confirmatory trial before Accelerated Approval is granted. Currently, companies often start confirmatory trials after Accelerated Approval is granted, which leads to delays in granting traditional approval.

Advances in cancer care that prolong the lives of millions of cancer survivors are a major underlying reason for the increasing reliance on Accelerated Approvals for cancer therapies. This is because it is taking more time to demonstrate improvements in overall survival as patients live longer. However, there is ongoing concern that early endpoints do not always correlate with overall survival (776). One potential driver of this discordance is the way in which doses of new drugs are selected. Traditionally, cancer drug doses have been determined by escalating the dose given to patients until it is no longer tolerable. This strategy is less useful for targeted therapies and immunotherapies because they may be most effective and result in less severe side effects at doses lower than the "Maximal Tolerated Dose." To encourage selection of optimal doses of new drugs, FDA issued a draft guidance titled "*Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases*," in January 2023 (777). Additionally, a workshop in July 2023 co-organized by FDA, AACR, and the American Statistical Association titled "Overall Survival in Oncology Clinical Trials" convened experts from across the cancer research community to discuss best practices to improve how clinical trials collect and assess endpoint data. Some key recommendations for trial sponsors discussed during the workshop included: having a prospective plan to collect and analyze overall survival in all clinical trials, even if it is not the primary endpoint; considering the disease and treatment setting to determine how long data should be collected, instead of a standardized 5-year follow-up; and prioritizing recruitment of patients positive for predictive

A provision in the **Inflation Reduction Act** allows Medicare to implement price negotiation for small molecules after nine years, compared to 13 years for biologic therapies such as antibodies and cell therapies. There is concern among industry that this provision disincentivizes innovation for small molecules because it takes a similar amount of time and resources to develop both small molecules and biologics.

biomarkers for targeted and immunotherapies. Improvements in how cancer drugs are studied and doses are selected have the potential to accelerate the pace of progress against cancer.

Addressing Cancer Drug Shortages

In addition to ensuring that new cancer therapies are safe and effective, FDA is responsible for regulating the supply of drugs so that patients can get the medications they need. Unfortunately, there have been record shortages of cancer drugs this year. In December 2022, there were 295 prescription medications in short supply (778). Shortages of cisplatin and carboplatin are particularly impacting care options for patients, which are estimated to be prescribed for 10 to 20 percent of patients with cancer (779). The underlying causes of the shortages are varied and incredibly complex, and include supply chain disruptions, manufacturing quality issues, limited economic incentives to manufacture generic drugs, and increasing reliance on fewer manufacturers. To help alleviate the shortage of cisplatin, FDA issued a temporary authorization to import cisplatin from China. Congress has held several hearings this year to better understand the issue and identify potential solutions in coordination with the White House, FDA, and cancer-focused professional organizations (780).

FDA-NCI Collaborations to Promote Innovative Clinical Research

FDA and NCI have recently established several collaborations to promote innovation in clinical research. In February 2023, the Clinical Trials Innovation Unit (CTIU) was established to fund novel trial designs, with a focus on expanding access to historically underserved communities (781). This collaboration pairs funding from NCI and trial design advice from FDA with the goal of expanding trial eligibility, investigating new endpoints, utilizing streamlined data collection strategies, and other novel methods and technologies to improve equity in cancer research. Another collaboration created in 2019, called the Connecting Awardees to Regulatory Experts (CARE) program, is focused on small businesses funded by NCI to begin developing new therapies (782). The CARE program provides additional opportunities for NCI-funded small businesses to meet with FDA to discuss their development plans and promote successful regulatory submissions. From 2019 to 2022, 141 small businesses have participated in CARE, with 90 percent recommending the program to other companies.

Advancing Policy to Strengthen Cancer Prevention and Screening Programs

Approximately 40 percent of cancer cases in the United States can be attributed to preventable risk factors, such as tobacco use, infections, and UV exposure (see **Reducing the Risk of Cancer Development**, p. 38, and **Figure 24**, p. 162). Routine screenings using evidence-based approaches to detect common cancers greatly improve treatment options and outcomes (see **Screening for Early Detection**, p. 54). However, inequities remain in access to cancer screenings and follow-up care, which are major contributors to delayed diagnoses among underinsured and uninsured populations. CDC's National Breast and Cervical Cancer Early Detection Program and Colorectal Cancer Control Program provide routine cancer screenings for medically underserved populations across the United States. Funding limitations prevent these crucial programs from providing screening services to all eligible people. According to the most recent data available, 6.8 percent of eligible people receive cervical cancer screenings and 15 percent of eligible people received breast cancer screenings through these programs (783,784). Medicaid expansion has helped increase cancer screenings in medically underserved populations (785) and is

In 2023, close to 300,000 women in the United States will be diagnosed with invasive breast cancer and over 13,000 people will be diagnosed with invasive cervical cancer. **Reauthorization of the Screening for Communities to Receive Early and Equitable Needed Services for Cancer Act is crucial** to continue to support the National Breast and Cervical Cancer Early Detection Program.

another substantive approach for advancing health equity (786). Thus, additional federal investment for these programs would improve equity in cancer screening, follow-up care, and advance the goals of the Cancer Moonshot, as underscored by **Senator Robert P. Casey, Jr.**, p. 160.

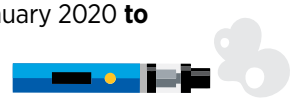
HPV infections can lead to six types of cancer, including nearly every case of cervical cancer (see **Prevent and Eliminate Infection from Cancer-causing Pathogens**, p. 48) (787). There are effective, evidence-based strategies that can prevent HPV-attributed cancers, such as guideline-concordant HPV vaccination, cervical cancer screenings, and timely follow-up care (see **Sidebar 15**, p. 49). Although HPV vaccination coverage increased among adolescents 13 to 17 years old in 2021 (215), there is still progress to be made to reach the Healthy People 2030 full vaccination goal of 80 percent in adolescents (217). Eliminating HPV-attributed cancers will only be achieved by coordinated strategies among all stakeholders to build confidence in vaccination and improve screening and treatment for HPV-related lesions.

Leveraging Policy to Reduce Tobacco-related Illness

Decades of public health awareness campaigns and effective tobacco control policies have resulted in historically low smoking rates among adults in the United States. In 2021, 18.7 percent of U.S. adults regularly used any tobacco product (32), and 11.5 percent of adults regularly smoked cigarettes. Despite the progress made against tobacco use among adults, tobacco product use during adolescence is still cause for great concern as this greatly increases the risk of nicotine dependence later in life. Results from the most recent National Youth Tobacco Survey indicate that 16.5 percent of high school and 4.5 percent of middle school students currently use any tobacco product (788). E-cigarettes remain the top choice for youth under the age of 18, with 14.1 percent of high school students reporting e-cigarette use and 3.3 percent of middle school students reporting e-cigarette use. Additional tobacco control policies across all levels of government remain important to continue reducing tobacco-related cancers as smoking remains the number one preventable cause of cancer (see **Figure 24**, p. 162).

In September 2022, FDA Commissioner Robert Califf, M.D., MACC requested an independent, operational evaluation of the FDA Center for Tobacco Products (CTP) to ensure the Center is prepared to address the impending challenges associated with youth tobacco use, tobacco-attributed disease, and death.

The **sale of e-cigarettes increased** from 15.5 million units in January 2020 **to 22.7 million units** by December 2022 .



FDA Center for Tobacco Products collects **tobacco user fees** from manufacturers of 6 traditional tobacco products: cigarettes, cigars, snuff, roll-your-own tobacco, chewing tobacco, and pipe tobacco. These fees, **totaling close to $710 million** annually, **fund all FDA tobacco regulatory activities**. Although FDA is authorized to regulate e-cigarettes, the agency is not allowed to collect user fees from e-cigarette manufacturers. Funds from other regulatory efforts are used, contributing to delays in regulation and enforcement.

The report from the Reagan-Udall Foundation for the Food and Drug Administration provided 15 recommendations, across multiple areas, to strengthen CTP's response towards the rapidly changing tobacco product landscape (790). In alignment with report recommendations, FDA and NIH awarded funding for a new Center for Rapid Surveillance of Tobacco, which will enhance CTP's and the research community's ability to understand, track, and assess changes in tobacco use and the product marketplace (791).

Further policies that could reduce tobacco-related illness include expanding flavor prohibitions to all tobacco products beyond e-cigarettes; increasing restrictions on tobacco product advertising and promotions; and increasing funding for awareness and cessation programs within FDA, NCI, and CDC's Office on Smoking and Health.

Accelerating Progress Against Pediatric Cancer

Cancer is the leading disease-related cause of death in children in the U.S. Each year, more than 15,000 children and adolescents under 19 years of age are diagnosed with cancer (792). Due to advances in treatments, about 80 percent of children survive their diagnoses. The overall cancer death rate for children under 14 years of age has declined an average of 1.5 percent per year between 2015 and 2019 (325). Nonetheless, cancer diagnosis continues to be devastating news for affected children and their families. Chronic conditions resulting from pediatric cancer treatments can continue

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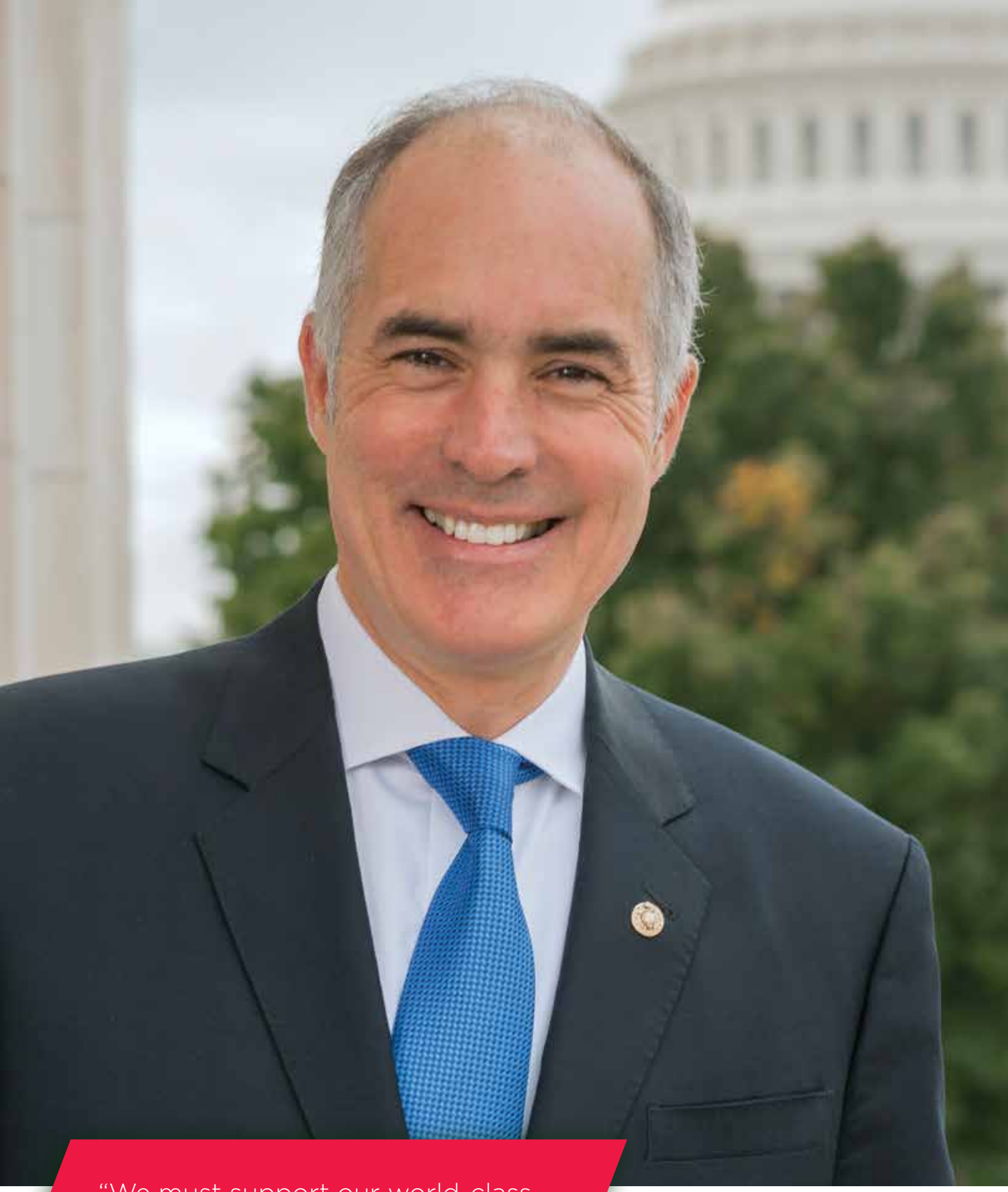


"We must support our world-class researchers working tirelessly every day to find a breakthrough and save lives."

U.S. SENATOR
Pennsylvania

CONGRESSIONAL CHAMPION OF CANCER RESEARCH

THE HONORABLE
Robert P. Casey, Jr.

You were diagnosed with prostate cancer in January 2023 and underwent successful surgery in February 2023. Could you share how your cancer journey has influenced your work in Congress?

When I was diagnosed with cancer, I was fortunate to have an excellent prognosis and access to exceptional medical care. My recommended course of treatment was straightforward and, following a successful surgery on Valentine's Day, my doctor confirmed that I don't require further treatment. Millions of Americans aren't so lucky. In Congress, I'm fighting to ensure every single American has access to world-class health care that doesn't bankrupt themselves or their family. Affordability or access should never stand in the way of someone getting the care they need.

How has that personal experience shaped your approach to health policy and the importance of funding for cancer screening, prevention, and research?

I know from personal experience that regular cancer screenings and access to preventative health care can save lives. We must encourage Americans to regularly see their health care providers and receive recommended cancer screenings, and we need to make it easy and affordable to do that, especially for those in underserved communities. We also need to invest in cancer research to further treat and prevent cancer in the future.

Which policy priorities or legislative efforts do you share that would fuel better prevention, detection, and treatment of cancer?

Every year, I lead the charge in the Senate for robust funding for the National Institutes of Health, which includes the National Cancer Institute. Ensuring entities like the NIH have the funding necessary to continue advancing the science of cancer prevention, detection, and treatment is critical to the nearly two million people that are diagnosed with cancer each year. We must support our world-class researchers working tirelessly every day to find a breakthrough and save lives.

Americans also need health insurance that will allow them to afford cancer screenings and treatment. I've always been committed to defending and expanding access to Medicaid, Medicare, and marketplace plans as well as ensuring that cost is not a barrier to getting health care; my cancer diagnosis gave me a more personal stake in that fight.

Finally, it's unacceptable that where people lives or how much money they make can be the difference between life and death in cancer cases. Last Congress, I introduced and passed legislation to expand the reach of community health workers, which helps connect people in underserved communities with quality health care and other supports to improve health and well-being, because health equity is a priority to me and we must continue to advocate for people and strategies that will help us combat health disparities.

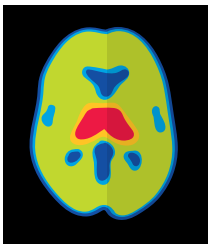
What is your message to the scientists and physicians working to make progress against cancer?

Thank you for your tireless work in the fight against cancer. It's your commitment to better understand and treat cancer that gives me hope for a future where cancer diagnosis has much less of an impact than it does today. Know that I will continue to advocate on your behalf to ensure that you have the support and resources needed to do the work that will ultimately save lives.

FIGURE 24

How Flavored Tobacco Products Contribute to Disparities

Masks Harsh Taste

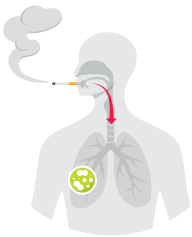


Menthol Increases Nicotine Receptors

Youth More Likely to Try

Cooling Effect of Menthol Hides Smoke Irritation

Predatory Marketing



Tobacco Smoke Causes 17 Types of Cancer Beyond Lung

The tobacco industry has used flavored products and predatory marketing practices, such as providing free samples of menthol cigarettes, to attract racial and ethnic minority communities to nicotine for decades.

These aggressive campaigns were intentional business strategies to preserve market share as overall smoking rates dropped across the United States.

to impact survivors into adulthood, and families of young people with cancer frequently endure emotional and financial hardship.

An important development in the fight against pediatric cancer is the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act. Enacted in 2018, the Childhood Cancer STAR Act aims to improve health outcomes of young patients with cancer and advance pediatric cancer research by:

- Awarding grants to state cancer registries to improve surveillance for pediatric cancer.
- Supporting efforts to expand collection of biospecimens and clinical information on pediatric cancer patients to support research on childhood cancer and survivorship.
- Creating programs to explore innovative care models for childhood cancer survivors.

In January 2023, President Biden signed into law the Childhood STAR Reauthorization Act (793), allowing programs from the STAR Act to continue through FY 2028 at its fully authorized level of $30 million, as discussed by **Congressman Michael T. McCaul**, p. 164. The reauthorization also supports funding of the Childhood Cancer Data Initiative (CCDI) at $50 million, which helps children's hospitals, clinics, and other facilities share clinical and research data. Created in 2019, the CCDI works to improve understanding of pediatric cancer biology, prevention, treatment, and survivorship through enhanced data sharing.

However, the Childhood Cancer STAR Reauthorization Act only provides legal authority for programs created by the law to continue. As a next step, pediatric cancer advocates must ensure that Congress fully funds the Childhood Cancer STAR Act and the CCDI during the FY 2024 appropriations process.

Another program crucial to advancing progress against childhood cancer is the Gabriella Miller Kids First Pediatric Research Program (Kids First). Established in 2015, Kids First aims to help researchers make new discoveries into the biology of pediatric cancer as well as the relationship between structural birth defects and certain types of childhood cancer. Between 2015 and 2022, Kids First selected 63 pediatric cancer and structural birth defects cohorts for whole genome sequencing that entails more than 20,000 patients and 55,000 genomes (794).

Kids First is set to sunset at the conclusion of FY 2023. To build on the program's success in accelerating childhood cancer research, a bipartisan group of lawmakers introduced the Gabriella Miller Kids First Research Act 2.0 (H.R. 3391) (795). In addition to reauthorizing Kids First through FY 2027, the Gabriella Miller Kids First Research Act 2.0 would nearly double funding for the program to $25 million annually. The House passed an earlier version of the Gabriella Miller Kids First Research Act 2.0 in July 2022, but insufficient support in the Senate and a limited Congressional calendar prevented the legislation from moving forward. Fortunately, lawmakers from both parties have reintroduced the Gabriella Miller Kids First Research Act 2.0 in Congress, breathing new life into this important vehicle for improving the lives of the nation's youngest patients with cancer.

Aside from medical research, health care coverage remains an important issue for children facing cancer. Nearly half of all children in the U.S. have health insurance coverage through Medicaid or the Children's Health Insurance Program (CHIP) (796). However, millions of children face the prospect of losing their insurance coverage as flexibilities permitted because of the COVID-19 pandemic expire. Since March 2020, the federal government has provided state Medicaid offices additional Medicaid funding in exchange for ensuring continuous coverage of Medicaid enrollees and suspending eligibility determination processes. These emergency coverage protections for Medicaid enrollees ended on April 1, 2023, and the federal government has allowed state Medicaid agencies up to 14 months to redetermine the eligibility of enrollees, including children. While outcomes of the redetermination process will vary from state to state, an estimated 6.7 million children could lose their coverage and face prolonged periods without insurance (796). These coverage losses would be especially devastating to children undergoing cancer treatment and their families. Thus, it is crucial for policymakers to ensure that state Medicaid agencies have the guidance and resources available to limit coverage losses and connect children who have lost Medicaid or CHIP coverage with new coverage options.

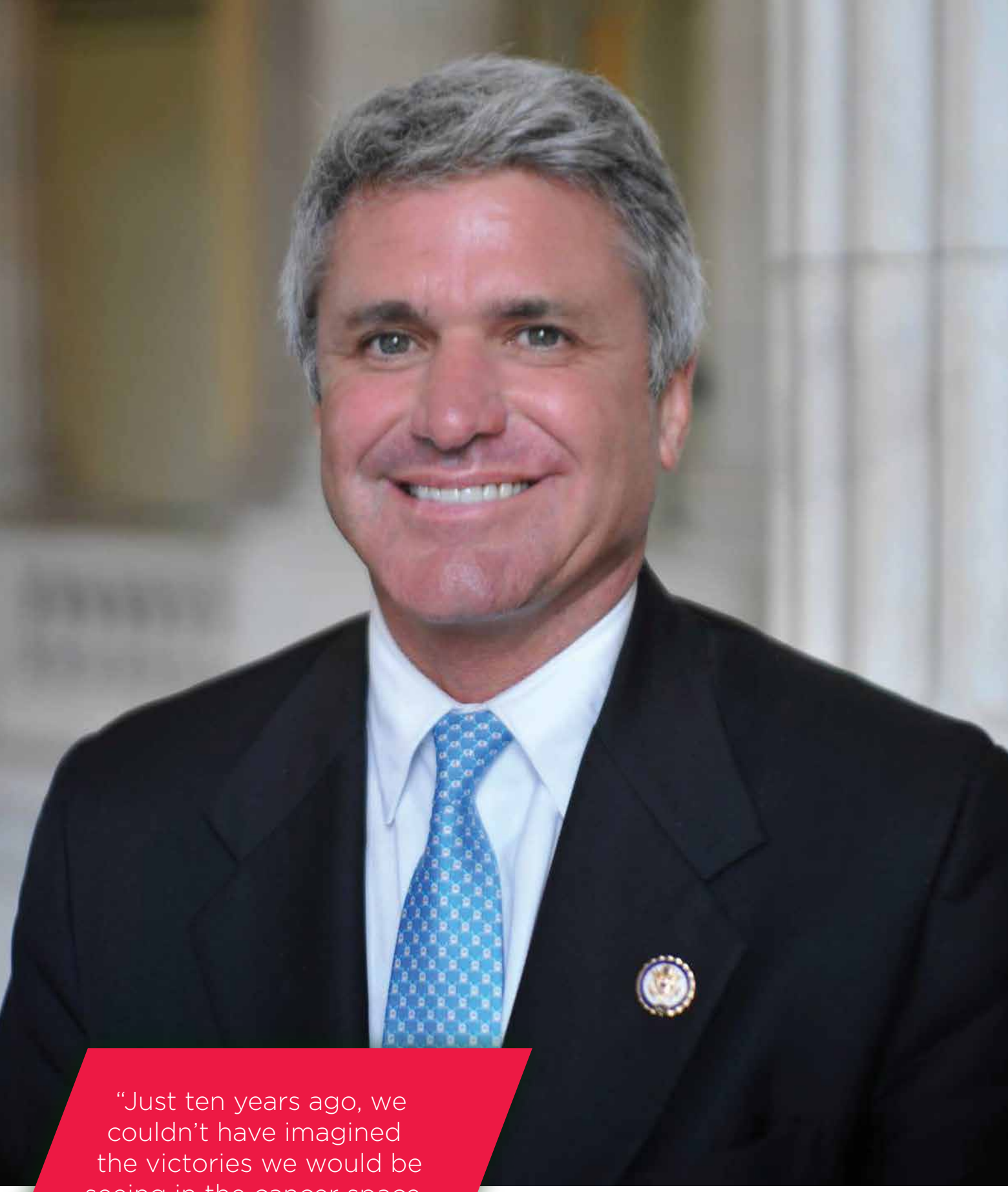
Building Health Equity by Addressing Cancer Disparities

As described in the *AACR Cancer Disparities Progress Report 2022* (13), systemic disadvantages greatly contribute to poorer health outcomes for medically underserved communities. Centuries of discriminatory policies that restrict housing, education, and employment opportunities for racial and ethnic minorities have led to lower health insurance coverage rates, lower utilization of preventive health services, poor nutrition, and inadequate access to quality health care. Additionally, the lack of high-quality health care facilities in low-income neighborhoods and rural communities results in a lower quality of care even for those who can afford it. Eliminating cancer disparities will require a long-term, multipronged approach that supports individuals, communities, health care centers, and federal agencies, as well as local, tribal, and state governments. Recent policy developments related to cancer screening, nutrition, and health insurance have demonstrated that work in addressing health disparities is underway, but there is still more progress that must be made (see **Sidebar 3**, p. 18).

In June 2023, NCI awarded $50 million **to create five new Centers for Cancer Control Research in Persistent Poverty Areas** under the Persistent Poverty Initiative, which aims to address the factors behind persistent poverty in the context of cancer (797).

Routine cancer screenings are necessary to detect precancerous and cancerous lesions as early as possible in cancer development; however, variability in cancer screening contributes to cancer disparities. Unfortunately, follow-up care is less likely to occur for patients from rural areas or from racial and ethnic minority backgrounds for many historic and systemic reasons, including being uninsured or underinsured, decreased access to care, health care system bias, and miscommunication with health care providers (see **Suboptimal Uptake of Cancer Screening**, p. 61).

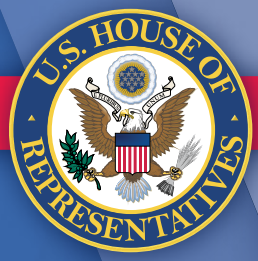
Several additional initiatives organized by NIH, NCI, the National Institute on Minority Health and Health Disparities (NIMHD), and CDC are designed to address cancer disparities. For example, NIH's All of Us program aims to improve precision medicine research by building one of the largest and most diverse health databases. To date, over 661,000 people have joined the research program. The NCI Community Oncology Research Program is a national network that brings cancer clinical trials and care delivery studies to people in their own communities. Additionally, the NCI Center to Reduce Cancer Health Disparities supports disparities research within NCI and reinforces training a diverse cancer research workforce. NIMHD is NIH's core institute to support research on the many factors that contribute to disparate health outcomes, including socioeconomics, politics, discrimination, culture, and environment (see **Figure 2**, p. 19). This work needs to continue and be adequately funded to urgently address cancer disparities. All research and clinical trials should be conducted with consideration for every patient. This means reaching out to and involving individuals in previously neglected regions of the country.



"Just ten years ago, we couldn't have imagined the victories we would be seeing in the cancer space today. I am confident that in another ten years, we'll be able to say the same."

U.S. REPRESENTATIVE
Texas's 10th District

CONGRESSIONAL CHAMPION OF CANCER RESEARCH



THE HONORABLE Michael T. McCaul, Sr.

Since joining Congress, and to honor your childhood friend who passed from cancer, you have been a steadfast advocate about the importance of cancer research. Could you share how your friend's battle against cancer, and those of others close to you, have influenced your work in Congress?

I was nine years old when I first learned about cancer. My fourth-grade classmate and best friend entered school one day, and I noticed his hair falling out. "I'm really sick," he told me when I asked what was going on.

One month later, I attended his funeral. That's when I discovered the devastation cancer can cause. I barely understood how such a thing could happen, but I knew I wanted to keep it from happening to other kids. That's why I founded the Childhood Cancer Caucus as soon as I joined Congress, with the mission of eliminating cancer as a threat to all children.

How has that personal experience shaped your approach to health policy and the importance of funding for cancer screening, prevention, and research?

Throughout my time in Congress, I've gotten to know many brave cancer patients and survivors. They are without a doubt my biggest inspiration. My friend Sadie, for example, was diagnosed with leukemia in 2015 at the age of seven. Since then, she has overcome cancer and gone on to advocate for countless other patients. She and I even wrote a book together about her journey and our work to pass new childhood cancer laws.

Another one of my favorite young fighters is named Sophie. When I first met her—three months before my annual Childhood Cancer summit—she was blind and confined to a wheelchair. But she had the biggest smile and the strongest spirit. Her family enrolled her in natural killer cell therapy, a form of immunotherapy only recently available to children. And when my summit came around just three months later, she could see and walk with support.

Her story is becoming more and more common, as our caucus continues pushing for increased research and new treatments to be made available for children. In fact, Sophie's form of immunotherapy was made possible by a clinical trial at M.D. Anderson that used the voucher system established by my Creating Hope Act. Once you see these life-changing results right in front of your eyes, it's impossible not to fight for more funding, research, and treatments for other patients.

What is your message to the scientists and physicians working to make progress against cancer?

Keep going! Today's research and innovation are leading to exciting possibilities, ranging from new cancer vaccines to natural killer cell therapy.

I recently met with a beautiful little girl named Ailani, who is fighting a rare form of leukemia (although you wouldn't know it from looking at her radiant smile). Ailani is enrolled in a clinical trial for a CAR T-cell therapy that her parents tell me would have been unthinkable just last decade.

Given the incredible advances being made at hospitals and research facilities across the country—including M.D. Anderson and Texas Children's in my home state—I am extremely optimistic about what the future holds. Just ten years ago, we couldn't have imagined the victories we would be seeing in the cancer space today. I am confident that in another ten years, we'll be able to say the same.

Which policy priorities or legislative efforts do you share that would fuel better prevention, detection, and treatment of cancer?

I'm proud to have introduced and passed several bills that I believe are changing the landscape of childhood cancer research and innovation. The STAR Act, for example—the most comprehensive childhood cancer bill ever written—improves cancer surveillance, expands research, and provides resources to survivors. It has already been reauthorized for the next several years, and I hope Congress continues to authorize and fund this important initiative for years to come.

This session, I'm continuing to champion legislation titled the Give Kids a Chance Act. This bill would build on my RACE for Children Act, which directs drug manufacturers producing adult cancer drugs to study those same drugs for children. Since RACE was signed into law in 2017, there have already been 32 pediatric studies. However, children with relapsed cancer are rarely cured by one-drug treatments because their cancers are so advanced. And while thousands of successful drug combination therapies are now being studied and developed for adults, the FDA has only authorized pediatric cancer trials of single drugs. The Give Kids a Chance Act would authorize the FDA to direct companies to study combination drugs and therapies in pediatric trials as well. I'll never stop fighting to give both children and adults every opportunity to beat cancer.

Conclusion

The annual AACR Cancer Progress Report, currently in its thirteenth edition, is a cornerstone of AACR's educational efforts to disseminate the knowledge of groundbreaking advances against cancer to the American public, policymakers, and the scientific community.

The *AACR Cancer Progress Report 2023* continues the tradition of documenting the unprecedented progress against cancer and underscoring how continued investments in cancer research will ensure that treating and curing all cancers is within our reach. Cancer-related deaths are continuing to decline at a steady pace. Breakthroughs in discovery science, and innovative technologies that enable them, are revolutionizing the ways we prevent, detect, and treat cancer. Advances in understanding the molecular underpinnings of cancer at a single cell level are unraveling the complexities of the disease. Precision medicine is expanding our ability to successfully treat previously intractable types of cancer. Immunotherapy, the exciting new frontier in precision medicine, is harnessing the power of the immune system to treat more types of cancer.

The result is an astounding 3.8 million lives saved from cancer since 1991, and more than 18 million cancer survivors living in the U.S. as of January 2022. Just in the 12 months covered by this report (August 1, 2022, to July 31, 2023), FDA approved 14 new anticancer therapeutics and expanded the use of 12 previously approved anticancer drugs to treat new types of cancer. The remarkable strides in cancer immunotherapy are exemplified by the effectiveness of immune checkpoint inhibitors (ICI) in treating different types of cancer. In January 2013, there was only one FDA-approved ICI to treat just one cancer type. In a decade since, and as of July 31, 2023, there were 11 FDA-approved ICIs. There is at least one ICI approved for treating at least one of 20 different types of cancer and any type of solid tumor characterized by the presence of certain specific molecular characteristics. As we envision a future where all cancers are successfully treatable and have a higher likelihood of being cured, new frontiers in cancer science and medicine, such as the use of artificial intelligence and liquid biopsy, and the development of vaccines to treat cancer, are bringing excitement within the cancer care community for what is possible in reducing the burden of cancer.

As we celebrate the contributions of medical research to the current knowledge of how we detect and treat cancer and applaud all stakeholders in cancer research and patient care whose tireless work has made progress against cancer possible, we must also realize that much work still needs to be done. Achieving the goal of health equity where successful treatments for cancers are accessible to all populations, will not be possible without addressing systemic and socioeconomic inequities that place a disproportionate burden of cancer on medically underserved populations. We must implement public health policies to raise the awareness of risk factors that increase an individual's likelihood of developing cancer, so that, among other risk factors, the rising rates of obesity in the U.S. population and e-cigarette usage among U.S. youth can be reduced. We must enact evidence-based interventions to remove barriers that prevent individuals from the receiving recommended cancer screening and/or follow-up testing, so that cancers are detected at the earliest possible stage when it is easier to successfully treat them. We must inform and educate patients with cancer about the benefits of participating in clinical trials, so that the findings of these studies have the potential to benefit all patients. We must ensure that quality health care is available and accessible to everyone, so that patients with cancer and their caregivers are not adversely affected by the financial burden from a cancer diagnosis. With the continued resolve of all stakeholders, and consistent Congressional support for medical research, these challenges are addressable, and mitigating them will have a profoundly positive and long-term effect on the physical, psychosocial, and financial health of our nation.

Investments in NIH and NCI over the past two decades have yielded an immense return, as is evidenced by the fact that the $36.68 billion dollars NIH awarded in funding during the fiscal year 2022 supported more than half a million jobs and generated nearly $97 billion in economic activity across the nation. Based on the evidence presented in the report, AACR urges Congress to continue its unwavering and historically bipartisan support to make medical research a long-term strategic priority for our nation (see **AACR Call to Action**, p. 167). All stakeholders in the cancer research and care community can seize today's unprecedented scientific opportunities to advance the frontiers of cancer science and medicine for the benefit of all patients with cancer.

AACR Call to Action

Since FY 2015, the medical research community has been fortunate to receive eight consecutive years of funding increases for NIH. These funding increases have coincided with a decline in cancer mortality in the United States. Between 2015 and 2019, overall cancer death rates declined by 2.1 percent per year in both men and women. The drop in cancer mortality within this period comes amid a longer, multidecade trend towards fewer cancer deaths. As of 2020, the overall cancer mortality rate had decreased by 33 percent from its highest level in 1991 (2). In addition to breakthroughs in therapies, these declines can be attributed to improvements in cancer prevention and early detection.

As cancer mortality rates decline, the number of cancer survivors is estimated to increase to 26 million by 2040 (798). Forty-seven percent of cancer survivors have multiple chronic conditions (799), which leads to poorer quality of life and worse cancer outcomes. Thus, policymakers must support cancer survivors by enacting legislation to provide survivors of cancer the resources they need.

Further action is also needed to address the use of tobacco products. While the percentage of United States adults who use combustible tobacco products is at a record low, cigarette smoking remains the leading cause of preventable death in the U.S., contributing to nearly one in five deaths (800). Additionally, a growing number of American youth and young adults are taking up the use of electronic cigarettes. Electronic cigarettes still emit many harmful chemicals with unknown long-term health impacts. As the number of young adults who use e-cigarettes continues to grow, it is prudent that policymakers continue to support smoking prevention and cessation initiatives and programs to reduce use of e-cigarettes.

The new generation of therapies including novel immunotherapeutics, antibody-drug conjugates, combination therapies, cell therapies, and proteolysis targeting chimera technology has the potential to transform cancer treatment. However, strong federal investments in medical research, including through the newly created ARPA-H, are essential for discovering these treatments as well as to ensure that they become readily available to all patient populations. Therefore, policymakers must continue to provide robust, sustained, and predictable funding increases for NIH and NCI to ensure greater availability of promising cancer treatments.

Additionally, federal investments in medical research must continue to focus on reducing health inequities. Stronger investments in NIH and NCI can boost diversity in the cancer research workforce and enhance clinical trial diversity. Furthermore, higher appropriations for cancer programs at CDC can improve health equity by improving the availability of cancer screening and prevention programs across diverse communities.

AACR urges Congress to continue to support robust, sustained, and predictable funding growth for the federal medical research and health programs vital to the fight against cancer. We call on Congress to:

- **Increase the FY 2024 base budgets** of the NIH and NCI by at least $3.465 billion and $2.6 billion, respectively, for total funding levels of $50.924 billion for NIH and $9.988 billion for NCI.
- **Provide $1.7 billion in dedicated funding** for Cancer Moonshot activities in FY 2024 across NCI, FDA, and CDC with the assurance that Moonshot funding will supplement rather than supplant NIH funding in FY 2024.
- **Appropriate at least $472.4 million** in FY 2024 appropriations for the CDC Division of Cancer Prevention to support comprehensive cancer control, central cancer registries, and screening and awareness programs for specific cancers.
- **Allocate $50 million in funding** for the Oncology Center of Excellence at FDA in FY 2024 to provide regulators with the capable staff and necessary tools to conduct expedited review of cancer-related medical products.

By following through on these recommendations, Congress will help accelerate the rate of discovery, solidify our competitive edge in advancing science, and create a vital pathway for young scientists to contribute to future advances in cancer research. Ultimately, this will improve our nation's health, including the lives of the millions of individuals who have been touched by cancer.

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Glossary*

A

Adjuvant therapy Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Advanced Research Projects Agency for Health (ARPA-H) An independent, research funding agency entity within the National Institutes of Health that supports transformative biomedical and health breakthroughs.

Angiogenesis The process of growing new blood vessels from the existing vasculature. Angiogenesis is important for numerous normal body functions, as well as tumor growth and metastasis.

Antibody–drug conjugate A therapeutic comprising an antibody chemically linked to a cytotoxic chemotherapeutic. The antibody binds to specific proteins on the surface of certain types of cells, including cancer cells. The linked cytotoxic chemotherapeutic enters these cells and kills them without harming nearby cells.

Artificial Intelligence A phenomenon that leverages computers and machines to mimic the problem-solving and decision-making capabilities of the human mind, such as how to act, reason, and learn.

B

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

B-cell maturation antigen (BCMA) A receptor that plays an important role in regulating B-cell proliferation and survival. BCMA is expressed on the cell membrane of normal and malignant plasma cells, but not other normal tissues.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Biomedical Research and Development Price Index (BRDPI) A measure of how much the National Institutes of Health budget must change to maintain purchasing power. The BRDPI is updated annually.

Bispecific antibody A type of antibody that can bind to two different antigens at the same time. Bispecific antibodies are being studied in the imaging and treatment of cancer. They are made in the laboratory.

BRCA1/2 Genes that produce proteins that are involved in repairing damaged DNA. Females who inherit certain mutations in a *BRCA1* or *BRCA2* gene are at increased risk of developing breast cancer, ovarian cancer, and some other types of cancer. Males who inherit certain BRCA1 or BRCA2 mutations are at increased risk of developing breast cancer, prostate cancer, and some other types of cancer.

Breast cancer Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

C

Cachexia Loss of body weight and muscle mass, and weakness that may occur in patients with cancer, AIDS, or other chronic diseases.

Cancer A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinomas begin in the skin or in tissues that line or cover internal organs. Sarcomas begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemias arise in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the blood. Lymphomas and multiple myeloma originate in the cells of the immune system. Central nervous system cancers arise in the tissues of the brain and spinal cord. Also called malignancy.

Carcinogen Any substance that causes cancer.

Carcinoma A cancer that begins in the skin or in tissues that line or cover internal organs.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2023*. The NCI has been used as the primary source for most definitions.

Caregiver A person who gives care to people who need help taking care of themselves. Examples include children, the elderly, or patients who have chronic illnesses or are disabled. Caregivers may be health professionals, family members, friends, social workers, or members of the clergy. They may give care at home or in a hospital or other health care setting.

Centers for Disease Control and Prevention (CDC) A federal agency, within the U.S. Public Health Service of the Department of Health and Human Services, whose mission is to protect public health by preventing and controlling disease, injury, and disability. The CDC promotes healthy behaviors and safe, healthy environments. It keeps track of health trends, tries to find the cause of health problems and outbreaks of disease, and responds to new public health threats.

Cervical cancer Cancer that arises in the cervix (the area where the uterus connects to the vagina). The two main types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are caused by persistent infection with certain strains of human papillomavirus (HPV). Normal cells of the cervix do not suddenly become cancerous; they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

Chemotherapy The use of chemical substances to kill or slow the growth of cancer cells.

Chimeric antigen receptor (CAR) A receptor created in the laboratory that is designed to bind to certain proteins on cancer cells. It is then added to immune cells called T cells taken from cancer patients. This helps the T cells find and kill cancer cells that have a specific protein that the CAR is designed to bind to.

Chromosome Structure within the nucleus of a cell that contains genetic information (DNA) and its associated proteins. Except for sperm and eggs, nearly all nondiseased human cells contain 46 chromosomes.

Chronic myelogenous leukemia (CML) A slow-growing cancer in which too many myeloblasts—a type of immature blood cell that makes white blood cells called myeloid cells—are found in the blood and bone marrow. CML is usually marked by a chromosome change called the Philadelphia chromosome, in which a piece of chromosome 9 and a piece of chromosome 22 break off and trade places with each other. Also called chronic granulocytic leukemia and chronic myeloid leukemia.

Circadian rhythm The natural cycle of physical, mental, and behavioral changes that the body goes through in a 24-hour cycle. Circadian rhythms are mostly affected by light and darkness and are controlled by a small area in the middle of the brain. They can affect sleep, body temperature, hormones, appetite, and other body functions.

Click chemistry Describes a method of joining molecules together by using simple, practical chemical reactions to synthesize drug-like molecules or create scientific assays.

Clinical trial A type of research study that tests how well new medical approaches work in people. These studies test new methods for screening, preventing, diagnosing, or treating a disease. Also called clinical study.

Colonoscopy Examination of the inside of the colon using a colonoscope that is inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Colorectal cancer Cancer that forms in the colon or the rectum. More than 95 percent of colorectal cancers are adenocarcinomas that arise in cells forming glands that make mucus to lubricate the inside of the colon and rectum. Before a colorectal cancer develops, a growth of tissue or tumor usually begins as a noncancerous polyp on the inner lining of the colon or rectum. Polyps can be found—for example, through colonoscopy—and removed before they turn into cancer.

Computed tomography (CT) A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an X-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

COVID-19 A highly contagious respiratory disease that is caused by the SARS-CoV-2 virus.

Cytokine A type of protein that is made by certain immune and nonimmune cells and has an effect on the immune system. Some cytokines stimulate the immune system and others slow it down.

Cytokine release syndrome A condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR-T cells. Cytokine release syndrome is caused by a large, rapid release of cytokines into the blood from immune cells affected by the immunotherapy.

Cytotoxic An agent or substance that is toxic to living cells.

D

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

Diabetes A disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in elevated levels of glucose in the blood and urine.

Disability-adjusted life years (DALYs) The measure of overall disease burden, expressed as the number of years lost due to ill health, disability, or early death.

DNA mismatch repair DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage.

E

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

Endocrine therapy Treatment that adds, blocks, or removes hormones. For certain conditions (such as diabetes or menopause), hormones are given to adjust low hormone levels. Hormones can also cause certain cancers (such as prostate and breast cancer) to grow. To slow or stop the growth of cancer, synthetic hormones or other drugs may be given to block the body's natural hormones, or surgery is used to remove the gland that makes a certain hormone.

Epidermal growth factor receptor (EGFR) A protein found on the surface of some cells to which epidermal growth factor binds, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including many types of lung cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called ErbB1 and HER1.

Epigenetic mark A chemical modification of DNA and/or histones that can control the accessibility of genes. The collection of epigenetic marks across the entire genome is referred to as the epigenome.

Epigenetics The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Extrachromosomal DNA (ecDNA) A double stranded DNA molecule found in various organisms, including humans, that is separate from chromosomes and can be located either inside or outside of the nucleus of a cell. ecDNA can play roles in certain diseases including cancer.

F

Financial toxicity A term used to describe financial problems a patient has related to the cost of cancer care.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

Food and Drug Administration (FDA) An agency in the U.S. federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. The FDA also makes sure that drugs, medical devices, and equipment are safe and effective, and that blood for transfusions and transplant tissue are safe.

G

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA and most genes contain the information for making a specific protein.

Genetic testing A laboratory method that looks for changes in genes, gene expression, or chromosomes in cells or tissue of a person. These changes may be a sign of a disease or condition, such as cancer. They may also be a sign that a person has an increased risk of developing a specific disease or condition or of having a child or other family member with the disease or condition. Genetic testing may also be done on tumor tissue to help diagnose cancer, plan treatment, or find out how well treatment is working.

Germline mutation A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Also called germline variant.

Glioblastoma A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord.

Glioma A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

H

Health-related quality of life (HRQOL) An individual's or a group's perceived physical and mental health over time.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma A cancer of the immune system that starts in white blood cells called lymphocytes.

Hormone One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human development index A summary measure of average achievement in key dimensions of human development including lifespan, health span, knowledge accumulation, and having a quality standard of living.

Human epidermal growth factor receptor 2 (HER-2) A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ERBB2 and NEU.

Human immunodeficiency virus (HIV) The cause of acquired immunodeficiency syndrome (AIDS).

Human papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also plays a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

I

Immune checkpoint inhibitor (ICI) Type of immunotherapy that blocks immune checkpoint proteins from binding with partner proteins, which allow the body to recognize cancer cells.

Immune system A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from invading microorganisms and other foreign substances, destroys infected and malignant cells, and removes cellular debris. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines.

Immunotherapy Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, such as cancer.

Incidence rate The number of new cases per population at risk in a given time period.

Inflammation A normal part of the body's response to injury or infection. Inflammation occurs when the body releases chemicals that trigger an immune response to fight off infection or heal damaged tissue. Once the injury or infection is healed, the inflammatory process ends.

L

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Low-dose computed tomography (LDCT) A procedure that uses a computer linked to an X-ray machine that gives off a very low dose of radiation to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-D views of tissues and organs.

Lymph nodes See definition for lymphatic system.

Lymphatic system The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body. Also called lymph system.

Lymphocyte-activation gene 3 (LAG-3) A cell surface molecule with diverse biologic effects on T cell function. LAG-3 binds to proteins known as MHC class II and negatively regulates proliferation, activation and homeostasis of T cells, in a similar fashion to PD-1.

Lymphoma Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells.

Lynch syndrome An inherited disorder that increases the risk of developing colorectal cancer, endometrial cancer, ovarian cancer, and many other types of cancer, such as cancers of the stomach, small intestine, pancreas, bile duct, urinary tract, and brain, often before age 50. Lynch syndrome is caused by mutations (changes) in genes that affect DNA mismatch repair, a process that fixes mistakes that occur when DNA is copied. These genes are MLH1, MSH2, MSH6, PMS2, and EPCAM.

M

Machine learning A field of computer science that develops the processes by which computers are taught how to learn and perform certain functions without being specifically programmed to perform those functions. Machine learning involves analyzing very large amounts of information to improve a computer's ability to make decisions or predictions. Machine learning is a part of artificial intelligence (AI). In medicine, the use of machine learning and AI may help improve cancer screening and diagnosis and plan treatment.

Magnetic resonance imaging (MRI) A noninvasive medical test that produces detailed pictures of areas inside the body through the use of radio waves and a powerful magnet linked to a computer. MRI is particularly useful for imaging the brain, spine, soft tissue of joints, and inside of bones. Also called nuclear magnetic resonance imaging (NMRI).

Mammogram An X-ray of the breast that is used to look for early signs of breast cancer.

Melanoma Cancer that begins in melanocytes (cells that make the pigment melanin). These cancers may arise in a mole (skin melanoma), but they can also originate in other pigmented tissues, such as the eye (uveal melanoma) or the intestines (mucosal melanoma).

Metastasis The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

Microbiome Describes the community of organisms (fungi, bacteria, and viruses) that exists in a particular environment, such as a part of the body including the skin, gastrointestinal tract, or tumor.

Molecularly targeted therapy A type of treatment that uses therapeutics to target specific molecules involved in the growth and spread of cancer cells.

Morbidity Refers to having a disease, a symptom of disease, the amount of disease within a population, or the medical problems caused by a treatment.

Multicancer detection (MCD) assays A type of blood test that is being studied as a way to screen for many types of cancer at the same time. Multicancer detection tests work by measuring biomarkers, such as pieces of DNA, that cancer cells release into the blood as they die. These tests may help find cancer in parts of the body that are not easily accessible for physical exam or biopsy.

Multiple myeloma A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

N

National Cancer Institute (NCI) The largest of the 27 institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

National Institutes of Health (NIH) A federal agency in the U.S. that conducts biomedical research in its own laboratories; supports the research of nonfederal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of research investigators; and fosters communication of medical information.

Neoadjuvant therapy Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

Non-Hodgkin lymphoma A term for a large group of cancers that arise in B cells or T cells. Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Cutaneous T-cell lymphoma is one example of a T-cell non-Hodgkin lymphoma.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

O

Oncogene A mutated gene that has the potential to cause cancer. Proto-oncogenes are oncogenes before they become mutated.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

P

Palliative care Care given to improve the quality of life and help reduce pain in people who have a serious or life-threatening disease, such as cancer. The goal of palliative care is to prevent or treat, as early as possible, the symptoms of the disease and the side effects caused by treatment of the disease. It also attends to the psychological, social, and spiritual problems caused by the disease or its treatment.

Pandemic An outbreak of a disease that occurs over a wide geographic area across international boundaries and affects an exceptionally high proportion of the population.

Pathogen A bacterium, virus, or other microorganism that can cause disease. Also referred to as an infectious agent.

Patient navigator A person who helps guide a patient through the health care system. This includes help going through the screening, diagnosis, treatment, and follow-up of a medical condition, such as cancer. A patient navigator helps patients communicate with their health care providers, so they get the information they need to make decisions about their health care. Patient navigators may also help patients set up appointments for doctor visits and medical tests and get financial, legal, and social support. They may also work with insurance companies, employers, case managers, lawyers, and others who may have an effect on a patient's health care needs. Also called patient advocate.

Patient reported outcome (PRO) Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

Patient reported outcome measure (PROM) Standardized, validated tools used to measure patient reported outcomes (PROs).

Precision medicine In oncology, precision medicine refers to the tailoring of treatments to the individual characteristics—in particular, the genetics—of patients and their cancer.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells. When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD-1 acts as an immune checkpoint protein or brake.

Programmed death-ligand 1 (PD-L1) A protein on the surface of many cell types, including some tumor cells. When it attaches to PD-1 on the surface of T cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively.

Prostate cancer Cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Prostate-specific membrane antigen (PSMA) A protein that is usually found on the surface of normal prostate cells but is found in higher amounts on prostate cancer cells. PSMA may be used as a target in imaging to help find prostate cancer cells, especially those that may have come back or spread to other parts of the body.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Psycho-oncology An interdisciplinary field to address the physical, psychological, social, and behavioral aspects of the cancer experience for both patients and caregivers.

Q

Quality of life The overall enjoyment of life. In cancer care, the term refers to an individual's sense of well-being and ability to carry out activities of daily living.

R

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radionuclide Also called radioisotope, a radionuclide is an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. In cancer medicine, radionuclides are used in diagnostic tests to detect the spread of cancer using imaging as well as in therapeutics, called radiopharmaceuticals, to treat cancer.

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Renal cell carcinoma The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

Ribonucleic acid (RNA) RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins.

S

Sarcoma Type of cancer that begin in the bones and connective tissues such as muscle, fat, blood vessels, nerves, tendons, and the lining of joints.

Sarcopenia A condition characterized by loss of muscle mass, strength, and function in older adults. Older age, getting little or no exercise, and poor nutrition may increase the risk of sarcopenia. Sarcopenia may also occur in people with cancer.

Signaling pathway/signaling network A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it alters the activity of another molecule. This process is repeated until the last molecule is activated, and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help prevent cancer cell growth and kill cancer cells.

Social determinants of health are the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and grow older that can affect their health, well-being, and quality of life. These include economic policies and systems, development agendas, social norms, social policies, and political systems.

Sociodemographic index A number from 0 to 1 that identifies where countries or geographic areas sit on the spectrum of development. It combines rankings of per capita income, average education attainment, and fertility rates.

Somatic mutation An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. Also known as acquired mutations.

Spatial transcriptomics A technique to count the number of transcripts of a gene at distinct spatial locations in a cell or tissue which can be used to assign cell types to specific locations within a sample.

Splicing Process that involves the removal or "splicing out" of certain sequences referred to as intervening sequences, or introns. The final mRNA consists of the remaining sequences, called exons, which are connected to one another through the splicing process.

T

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Treatment resistance The failure of cancer cells to respond to a treatment used to kill or weaken them. The cells may be resistant at the beginning of treatment or may become resistant after being exposed to the treatment.

Triple-negative breast cancer A type of breast cancer in which the cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative, PR-negative, HER2-negative breast cancer.

Tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

Tumor microenvironment The cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

U

United States Preventive Services Taskforce (USPSTF) Independent, volunteer panel of national experts in disease prevention and evidence-based medicine that makes evidence-based recommendations about clinical preventive services.

Uveal melanoma A rare cancer that begins in the cells that make the dark-colored pigment, called melanin, in the uvea or uveal tract of the eye.

V

Vaccine A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

W

Wearable technology Any technology designed to be used while worn in close contact to the skin, which can detect, analyze, and transmit information to the wearer and other designated individuals.

Appendix

SUPPLEMENTAL TABLE 1

Surgeries for the Prevention of Cancer

GENETIC MUTATION	CANCER	TECHNIQUE	REMOVES
APC	Colon cancer	Colectomy	Colon/large intestine
BRCA1 or *BRCA2*	Breast and ovarian cancers	Mastectomy and salpingo-oophorectomy	Breasts, and ovaries and fallopian tubes
CDH1	Breast and stomach cancers	Mastectomy and gastrectomy	Breast and stomach
Mutations associated with Lynch syndrome	Colon, endometrial, and ovarian cancers	Colectomy, hysterectomy, and salpingo-oophorectomy	Colon/large intestine, uterus, and ovaries and fallopian tubes
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

SUPPLEMENTAL TABLE 2

Newly FDA-approved Anticancer Agents: August 1, 2022-July 31, 2023 (Extended Table)

TYPE OF TREATMENT	GENERIC NAME	WHAT IS IT?	APPROVED FOR?	CLINICAL TRIAL(S)	FORMULATION
Surgery, Chemotherapy, Radiotherapy	flotufolastat fluorine-18	Imaging agent	Certain type of prostate cancer	NCT04186819, NCT04186845	IV
	pafolacianine*	Imaging agent	Certain type of lung cancer	NCT04241315	IV
Molecularly Targeted Therapy	adagrasib§	Cell-signaling inhibitor	Certain type of lung cancer	NCT03785249	Tablet/Capsule
	fam-trastuzumab deruxtecan-nxki§	Antibody–drug conjugate	Certain type of lung cancer*	NCT04644237	IV
	selpercatinib	Cell-signaling inhibitor	Solid tumors carrying certain type of genetic mutation*	NCT03157128	Tablet/Capsule
	mirvetuximab soravtansine-gynx§	Antibody–drug conjugate	Certain type of ovarian cancer	NCT04296890	IV
	elacestrant	Antihormone	Certain type of breast cancer	NCT03778931	Tablet/Capsule
	futibatinib	Cell-signaling inhibitor	Certain type of bile duct cancer	NCT02052778	Tablet/Capsule
	dabrafenib + trametinib	Cell-signaling inhibitors	Certain type of glioma*	NCT02684058	Tablet/Capsule
	tucatinib + trastuzumab	Cell-signaling inhibitors	Certain type of colorectal cancer*	NCT03043313	Tablet/IV
	olutasidenib§	Epigenome modifying agent	Certain type of leukemia	NCT02719574	Tablet/Capsule
	quizartinib§	Cell-signaling inhibitor	Certain type of leukemia	NCT02668653	Tablet/Capsule
	pemigatinib	Cell-signaling inhibitor	Certain types of blood cancer*	NCT03011372	Tablet/Capsule
	pirtobrutinib	Cell-signaling inhibitor	Certain types of lymphoma	NCT03740529	Tablet/Capsule
	zanubrutinib	Cell-signaling inhibitor	Certain types of lymphoma*	NCT03336333, NCT03734016	Tablet/Capsule
	talazoparib	DNA repair inhibitor	Certain type of prostate cancer*	NCT03395197	Tablet/Capsule
Immunotherapy	tremelimumab + durvalumab	Immune checkpoint inhibitors	Certain type of liver and lung cancers	NCT03164616, NCT03298451	IV
	retifanlimab-dlwr	Immune checkpoint inhibitor	Certain type of skin cancer	NCT03599713	IV
	durvalumab	Immune checkpoint inhibitor	Certain type of gallbladder cancer*	NCT03875235	IV
	atezolizumab	Immune checkpoint inhibitor	Alverloar soft part sarcoma*	NCT03141684	IV
	nadofaragene firadenovec-vncg	Gene therapy	Certain type of bladder cancer	NCT02773849	IV
	teclistamab-cqyv	Bispecific antibody	Multiple myeloma	NCT03145181, NCT04557098	IV
	mosunetuzumab-axgb	Bispecific antibody	Certain type of lymphoma	NCT02500407	IV
	epcoritamab-bysp	Bispecific antibody	Certain type of lymphoma	NCT03625037	IV
	glofitamab-gxbm	Bispecific antibody	Certain type of lymphoma	NCT03075696	IV

*New cancer type approved 2022-2023
§Requires a companion diagnostic
IV, Intravenous

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AACR Initiatives Accelerating Cancer Research

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Mission

The mission of the AACR is to prevent and cure cancer through research, education, communication, collaboration, science policy and advocacy, and funding for cancer research. Through its programs and services, AACR fosters research in cancer and related biomedical science; accelerates the dissemination of new research findings among scientists and others dedicated to the conquest of cancer; promotes science education and training; and advances the understanding of cancer etiology, prevention, diagnosis, and treatment throughout the world.

Membership

- AACR has more than 54,000 members residing in 130 countries and territories.
- Members include laboratory, translational, and clinical researchers; other health care professionals; and cancer advocates who depend on AACR's programs and activities for the exchange of timely scientific information.
- With over 25,000 Associate members, AACR supports the education, training, and professional development of early-career cancer researchers/scientists, who are graduate students, medical students and residents, and clinical and postdoctoral fellows. Annual dues are not required for Associate members.
- Through the Diversity, Equity, and Inclusion efforts of AACR-Minorities in Cancer Research and AACR-Women in Cancer Research, AACR supports the professional development and career advancement of underrepresented minority and women scientists in cancer research.
- Open to any AACR member are Scientific Working Groups to explore expanded research opportunities and advance discoveries that lead to greater knowledge and understanding of cancer.

Publications

The AACR proudly publishes **10 scientific journals** of high quality, covering the full spectrum of cancer science and medicine, including the online-only, open access journal, ***Cancer Research Communications***.

Cancer Today® is a magazine for cancer patients and caregivers.

Leading Discoveries is a magazine highlighting AACR members, programs, and philanthropic initiatives.

Learn about the cancer survivors featured in the ***AACR Cancer Progress Report 2023***.

The ***AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care*** provides a comprehensive review of pandemic-related challenges to cancer science and medicine, and future opportunities to improve medical research and patient care.

Learn how racial and ethnic minorities and other underserved populations are among the groups in the United States that have long experienced cancer health disparities in the ***AACR Cancer Disparities Progress Report 2022***.

Other AACR publications include the ***AACR Annual Impact Report***;

and the blog ***Cancer Research Catalyst***.

AACR Grants Program

- AACR funds research directly, as well as in cooperation with numerous cancer-focused organizations. As the Scientific Partner of Stand Up To Cancer, AACR provides expert peer-reviewed grant administration and scientific oversight of team science and individual grants for cancer research projects that have the potential to improve patient outcomes.
- Since establishing its grants program in 1993, AACR has provided over $528 million in funding for cancer research projects.

Meetings

AACR hosts more than 30 scientific conferences and educational workshops annually. The largest of these events is the AACR Annual Meeting. The next AACR Annual Meeting will be held April 5-10, 2024 in San Diego, California.

Policy and Advocacy

- The AACR Office of Science Policy and Government Affairs actively communicates with legislators and policymakers about the value of cancer research and related biomedical sciences to reduce cancer-related morbidity and mortality. It also advocates for critical federal cancer research funding.
- The AACR Scientist↔Survivor Program® provides support for cancer survivors and their families

AACR Project GENIE®

AACR Project GENIE® is an open-source, international, pancancer registry of real-world data assembled through data sharing between 22 leading international cancer centers. The registry leverages ongoing clinical sequencing efforts at participating cancer centers by pooling their data to serve as an evidence base for the entire cancer community.

AACR Foundation

The AACR Foundation accelerates progress in the conquest of cancer by providing financial support for scientific research, education, and communication. The Foundation funds programs deemed by the AACR to be of the highest priority and impact. Eighty-six cents of every dollar donated goes directly to lifesaving cancer research.

Professional Development

AACR supports education and training of cancer scientists and clinicians and provides professional development opportunities and resources to enhance and advance their careers. AACR CancerCareers.org is one resource that offers unparalleled career services and opportunities to cancer biomedical researchers and to potential employers who seek to recruit them.