AACR American Association for Cancer Research®

AACR CANCER PROGRESS REPORT 2026

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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 65,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 143 countries and territories around the world. Presently, 34% of members live outside the United States and 20% of AACR's international members are located in countries building cancer research capacity. 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. The AACR publishes 10 prestigious, peer-reviewed scientific journals. Other AACR publications include *Cancer Today*, a magazine for cancer patients and caregivers; the annual *AACR Cancer Progress Report*; *AACR Cancer Disparities Progress Report*; *AACR Pediatric Cancer Progress Report*; *AACR Annual Impact Report*; *Leading Discoveries*, the AACR's awareness and donor magazine; and the blog, *Cancer Research Catalyst*. In addition, 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. 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 AACR, visit **AACR.org.**

Message From AACR

Cancer science and medicine stand at an inflection point. Decades of federally supported research have transformed cancer prevention, detection, treatment, and survivorship care, leading to a steadily declining overall cancer death rate in the United States (US) and longer, healthier lives for millions of patients. Yet these hard-won gains are now at risk. Growing uncertainty surrounding funding for medical research and proposals that could weaken the rigor and independence of the National Institutes of Health (NIH) grantmaking process threaten the nation's ability to sustain scientific innovation and deliver future breakthroughs.

As the world's first and largest professional organization dedicated to preventing and curing all cancers, the American Association for Cancer Research (AACR) remains steadfast in advocating for robust, sustained, and predictable federal investment in medical research. This 16th edition of the AACR Cancer Progress Report highlights the extraordinary advances against cancer that have been made possible through federal support that sparked new scientific discoveries and technological innovations. These advances have increased our fundamental understanding of the complexities of cancer and accelerated the rate at which this knowledge is harnessed to develop new and better approaches to clinical care.

During the past 12 months alone, many scientific breakthroughs have reached patients with cancer in the form of new treatments for their specific diseases. The report features personal experiences of several individuals who directly benefited from some of these cutting-edge therapeutics, underscoring the profound impact of research-driven advances on saving lives and improving quality of life.

Among the 11 new anticancer agents that were approved by the US Food and Drug Administration (FDA) between July 1, 2025, and June 30, 2026, are 10 molecularly targeted therapeutics that are part of the precision oncology revolution. A number of these are landmark approvals that demonstrate how innovative approaches to drug discovery and development are expanding the therapeutic repertoire for patients. These include the first molecularly targeted therapy for diffuse midline glioma, a rare, aggressive brain tumor that primarily affects children, adolescents, and young adults, the first proteolysis-targeting chimera (PROTAC) treatment that harnesses the cell's protein disposal system to eliminate breast cancer cells, and three new precision medicines for lung cancer.

Immunotherapy continues to transform cancer care, with recent FDA decisions broadening the patient populations who can benefit from these treatments. Among the advances highlighted in this report are the first approval of an immune checkpoint inhibitor for ovarian cancer and the first FDA-approved treatment to delay progression of high-risk smoldering multiple myeloma into active disease. Another notable advance is the first approval of a chimeric antigen receptor (CAR) T-cell therapy for marginal zone lymphoma, a rare blood cancer.

Despite the significant strides against cancer, there is a vital need for continued transformative research. This urgency is underscored by the sobering reality that in the United States cancer will claim more than one life every minute of every day this year. This number is predicted to grow considerably in the coming decades, largely because of the overall population growth as well as an increase in the number of people age 65 and older, the population at greatest risk for developing cancer. A similar trend is projected globally, with cancer incidence expected to increase by nearly 65 percent between 2024 and 2050.

As documented in the recently published *AACR Cancer Disparities Progress Report 2026*, racial and ethnic minority groups and other medically underserved populations in the United States, including those living in rural areas, continue to bear a disproportionate burden of cancer. AACR is fiercely committed to understanding and addressing the biological, structural, and social drivers of cancer disparities and to ensuring that achieving health equity through research, policy, and advocacy is a national priority.

Notwithstanding these challenges, the momentum of scientific discovery has never been greater. Emerging technologies are opening new frontiers in understanding, detecting, and treating cancer. Artificial intelligence is poised to transform the full spectrum of cancer science and medicine, spanning drug discovery and diagnostics through clinical decision-making. Patient-centric tools, such as minimally invasive liquid biopsies, promise to identify cancers at earlier, more treatable stages. Exciting advances in cancer vaccines hold the potential to prevent, intercept, and treat previously intractable diseases, such as pancreatic cancer. Meanwhile, next-generation molecularly targeted therapies, such as programmable RNA molecules, are expanding our ability to tackle some of the most elusive cancer targets. These innovations and others on

the horizon reaffirm that sustained investments in cutting-edge science and technologies can dramatically accelerate the pace of progress for the benefit of cancer patients.

Realizing the promise of today's discoveries and accelerating progress toward a future where cancer is preventable, detectable, treatable, and ultimately curable for all require a strong bipartisan commitment to sustain the nation's medical research enterprise. This *AACR Cancer Progress Report 2026* is both a chronicle of progress against cancer and a call to action to protect and strengthen NIH, the National Cancer Institute, FDA, and the Centers for Disease Control and Prevention through robust, sustained, and predictable federal investment, to support the next generation of cancer researchers, and to preserve a rigorous, independent, and merit-based federal grantmaking system. The evidence is indisputable. Decades of federal investment have transformed patient care, saved millions of lives, spurred the US economy, and generated extraordinary returns for the public. By sustaining this commitment, we can ensure that the next generation of scientific discoveries will bring lifesaving cures to the millions of people whose lives are affected by cancer.

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Executive Summary

Transformative advances in cancer prevention, early detection, treatment, and survivorship over the past several decades, fueled by sustained federal investment in medical research, have reshaped clinical care and public health, leading to substantial reductions in cancer mortality and improved survival for millions of patients. As the first and largest professional organization in the world dedicated to preventing and curing all cancers, the American Association for Cancer Research (AACR) is committed to advancing public understanding of cancer and advocating for robust, sustained, and predictable federal support for medical research. This Cancer Progress Report to Congress and the American public, now in its 16th edition, remains a cornerstone of AACR's educational and advocacy efforts.

For more than 15 years, the AACR Cancer Progress Report series has chronicled the extraordinary pace of scientific discoveries and demonstrated how sustained federal support has expanded treatment options, improved survival, and enhanced quality of life for patients with cancer. This year's report continues that tradition by highlighting recent breakthroughs that are transforming patient care, including the inspiring personal stories of the seven courageous individuals featured in this document. The report also underscores that the momentum of progress against cancer depends on the collective efforts of researchers, clinicians, patients, advocates, and other key stakeholders across the medical research community and the unwavering support for the National Institutes of Health (NIH) and the National Cancer Institute (NCI), US Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC), whose complementary roles have transformed cancer prevention and care.

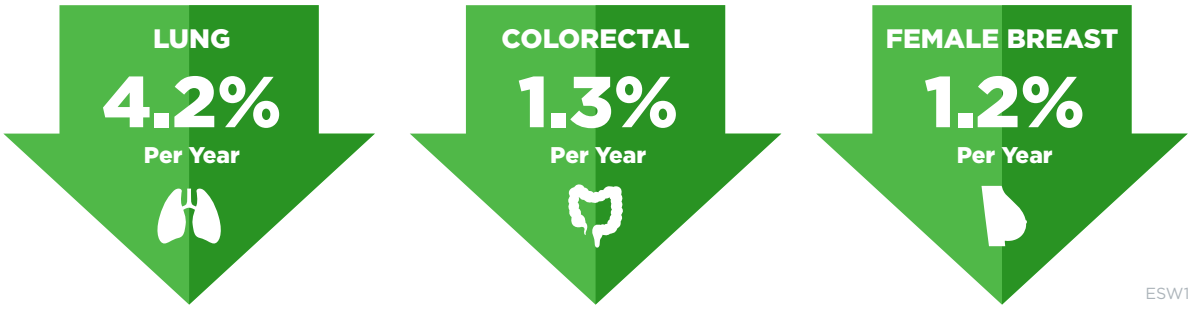
NIH- and NCI-funded foundational research has led to the innovations described throughout this report, laying the groundwork for the development of FDA-approved therapeutics and informing CDC-led cancer prevention programs. Growing uncertainty surrounding the future of federal investment in medical research, coupled with recent proposals to fundamentally alter how federal grants are awarded, poses a significant threat to NIH and its lifesaving mission to accelerate discoveries for patients with cancer and the hundreds of other diseases that affect millions of Americans. This report emphasizes the importance of preserving a rigorous and independent federal grantmaking process capable of delivering the next generation of lifesaving discoveries for all patients affected by this devastating disease.

Cancer in 2026

Remarkable progress against cancer has led to a steady decline in cancer mortality and an increase in the number of individuals living longer, fuller lives after a cancer diagnosis. In the United States, the overall cancer mortality rate declined by 35 percent between 1991 and 2024, resulting in more than 4.8 million cancer deaths averted.

The steady decline in overall US cancer mortality is largely driven by decreased smoking rates and subsequent declines in lung cancer deaths, a trend that has accelerated in recent years due to advances in early detection and treatment. Declines in death rates for colorectal cancer (CRC) and female breast cancer over the past three decades have also played a key role in reducing the overall US cancer mortality rate.

Average Annual Decline in US Death Rates for Selected Cancers (2015–2024)



Advances in precision medicine and immunotherapy have transformed the treatment landscape of several historically intractable cancers, including chronic myeloid leukemia, multiple myeloma, melanoma, and kidney cancer. These advances, and countless other breakthroughs across the continuum of cancer science and medicine, have led to an increase in the 5-year relative survival rate for all cancers combined, from 49 percent for those diagnosed with cancer in the mid-1970s to a record 71 percent among those diagnosed during 2016–2022.

Despite remarkable progress, cancer remains a major public health challenge in the United States and globally. An estimated 2.1 million new cancer cases will be diagnosed in 2026, and this number is projected to rise to 2.5 million by 2050. However, the burden of cancer is not distributed equally. Racial and ethnic minority groups and other medically underserved populations in the United States continue to shoulder a disproportionate burden of the disease. These disparities are driven by a complex interplay of social, economic, environmental, and structural factors that shape access to cancer prevention, early detection, timely treatment, and high-quality survivorship care.

Progress also remains uneven across cancer types and stages of disease. These differences are evident in 5-year relative survival rates, which vary widely by cancer type and stage at diagnosis. For patients diagnosed between 2016 and 2022, the overall 5-year relative survival rate was 14 percent for pancreatic cancer and 7 percent for glioblastoma multiforme, an aggressive brain cancer, compared to 92 percent for breast cancer and 98 percent for prostate cancer. The high overall survival rates for breast and prostate cancer, however, mask substantial differences by stage. For individuals with disease confined to the breast or prostate, the 5-year survival rate is nearly 100 percent, whereas for those with metastatic disease the rates are just 34 percent and 40 percent, respectively.

Additionally, changing cancer incidence patterns are causing new public health concerns. The incidence of several cancer types has been steadily increasing among individuals ages 18 to 49, a phenomenon known as early-onset cancer. Notably, this is the only age group to have experienced a sustained increase in overall cancer incidence between 1995 and 2021. The incidence of early-onset cancer has also grown disproportionately among females.

The burden of cancer and its economic impact on individuals and the US health care system are expected to rise in the coming decades, underscoring the urgent need for robust federal investment in research across the cancer continuum. However, recent funding cuts and proposed budget reductions are threatening to slow scientific progress, delay future discoveries, weaken the medical research workforce, and jeopardize future advances for individuals with cancer. Sustained and predictable federal investment in NIH, NCI, FDA, and CDC is essential to accelerate progress against cancer, preserve US leadership in medical research, support the next generation of cancer researchers, and ensure that future breakthroughs translate into longer, healthier lives for all people.

Understanding the Path to Cancer Development

Decades of basic research have established cancer as a collection of diseases characterized by the uncontrolled growth of cells. Cancer is driven by disruptions to the molecular and cellular functions that regulate how cells grow, divide, and survive. Many of these changes are often the first step in a complex, multistep process that is influenced by changes both inside and outside the cell.

Research has shown that different cancer types share certain characteristics or hallmarks, including the ability of cancer cells to divide limitlessly, disrupt normal regulation of cell growth, change identity and behavior, rewire metabolism to support rapid growth, resist cell death, stimulate blood vessel formation, evade the immune system, and leave the tissue of origin and spread to other organs.

Hallmarks of Cancer Cells

- Spread to other parts of the body
- Divide indefinitely
- Increase blood vessel formation toward tumor
- Evade the immune system
- Change identity and behavior
- Disrupt normal regulation of cell growth
- Resist cell death
- Rewire metabolism for growth

ESW2

Genetic alterations include changes in the DNA sequence that can disrupt or modify normal protein function and may contribute to cancer development. Genetic mutations associated with cancer can be either inherited (germline) or acquired during a person's lifetime (somatic). Germline mutations are passed down from parents to children and contribute to about 10 percent of all cancer cases. The remaining 90 percent of all cancer cases stem from somatic mutations, which can be acquired as a result of DNA damage, errors during normal cell division, or in response to environmental exposures, lifestyle factors, or chronic health conditions. Other changes inside the cell include RNA variations, protein modifications, and epigenetic alterations and often work together to drive cancer initiation and progression.

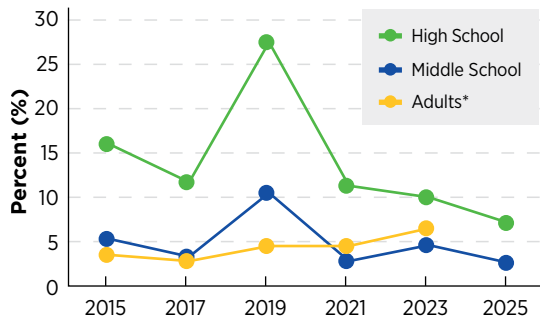
Influences outside the cell also play a critical role in cancer development. These external factors include the blood and lymphatic systems, the immune system, the nervous system, and the microbiome. As the disease progresses, cancer cells acquire additional characteristics that allow them to shape and respond to their surroundings, creating a dynamic biological system known as the tumor microenvironment (TME) that influences tumor growth, metastasis, and response to treatment.

Technological advances have made it possible to study cancer at unprecedented cellular and molecular resolution, revealing that each patient's cancer is unique. This foundational insight has paved the way for precision medicine, also called personalized medicine, which is broadly defined as using information about a person's genes, proteins, environment, and lifestyle to prevent, diagnose, or treat disease. Rapid advances in technologies, including artificial intelligence (AI) and large-scale collaborative research, are enabling researchers to integrate diverse biological and clinical data to make more accurate diagnoses, refine treatment selection, predict and monitor treatment response, and accelerate the development of more personalized cancer therapies.

Reducing the Risk of Cancer Development

Modifiable risk factors account for nearly 40 percent of all new cancer cases diagnosed in the United States, with tobacco use, excess body weight, and alcohol consumption responsible for a substantial proportion of this burden. Our understanding of cancer risk factors and cancer prevention strategies continues to evolve as new evidence identifies both the emerging risk factors and novel interventions. While tobacco use remains the leading preventable cause of cancer, emerging areas of research and public health concern include the increasing use of electronic cigarettes (e-cigarettes), the rapid uptake of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to combat obesity, and the growing recognition of chronic stress as a biologic and behavioral contributor to cancer risk and outcomes.

E-cigarette Use Among US Adults and Youth (2015–2025)



* No data available for 2025.

ESW3

National tobacco control policies and programs have dramatically reduced smoking prevalence and the associated cancer burden in the United States. Adult cigarette smoking declined from 42.4 percent in 1965 to a historic low of 9.9 percent in 2024, marking the first time smoking prevalence has fallen into single digits and bringing the nation closer to the Healthy People 2030 initiative target of 6.1 percent.

Despite this progress, the rise of e-cigarettes presents a new public health challenge. Although e-cigarette use has declined among youth in recent years, it remains the most commonly used tobacco product among middle and high school students, with nearly 6 percent reporting current use in 2025. Growing evidence suggests that e-cigarettes are not risk-free. While generally emitting fewer carcinogens than combustible cigarettes, e-cigarettes expose users to numerous toxic chemicals and metals that can damage DNA and promote inflammation. Recent research indicates that compounds released during e-cigarette use may increase the risk of lung, bladder, and other cancers, highlighting the need for continued surveillance and prevention efforts.

Obesity is associated with the increased risk of many cancers and continues to be highly prevalent among US children and adults. Increasing use of GLP-1 RAs for obesity and type 2 diabetes mellitus has generated considerable interest in their potential impact on reducing obesity-related cancer risk. Findings from several studies suggest that GLP-1 RA use reduces the risk of certain obesity-related cancers, with reported reductions in breast, colorectal, esophageal, endometrial, ovarian, and gastrointestinal cancers. However, some studies have shown no overall reduction in obesity-related cancers, and other evidence has raised concerns about potential increases in specific cancers, including kidney, thyroid, and respiratory cancers. Current evidence suggests that while GLP-1 RA therapies are effective for weight management and metabolic control, their long-term role in obesity-related cancer prevention warrants further investigation.

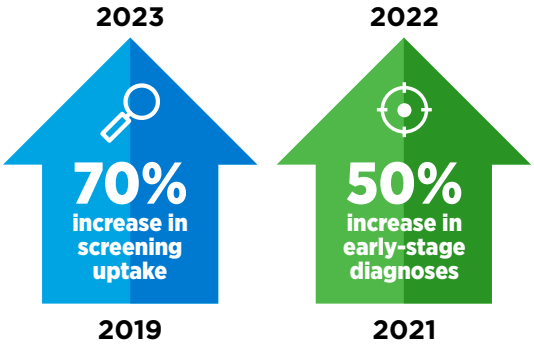
Chronic stress is emerging as a potentially important and modifiable contributor to cancer risk, progression, and outcome. Chronic stress results from ongoing exposure to adverse social, environmental, and economic conditions, including financial hardship, housing instability, discrimination, neighborhood violence, and food insecurity. Repeated activation of physiologic stress responses can lead to elevated allostatic load—a biologic measure of cumulative wear and tear across neuroendocrine, immune, metabolic, and cardiovascular systems. Studies have linked chronic stress and stress-related disorders to increased risks of breast, lung, colorectal, prostate, and hematologic cancers, as well as poorer cancer outcomes. Chronic stress may also indirectly increase cancer risk by promoting unhealthy coping behaviors such as tobacco use, alcohol consumption, physical inactivity, and poor dietary habits.

Cancer Screening for Early Detection

Cancer screening helps detect cancer or abnormal cells that might become cancerous in people without any symptoms of the disease. Screening also includes follow-up care if something abnormal is detected. Detecting cancer early when it is more treatable increases the chances of better outcomes. Evidence has firmly established routine cancer screening as a key approach to reducing the overall burden of cancer at the population level. As one example, an analysis of nine randomized trials covering nearly 830,000 people found flexible sigmoidoscopy cut CRC deaths by 26 percent.

The US Preventive Services Task Force (USPSTF), an independent expert panel, issues screening guidance for cancers of the breast, cervix, colon and rectum, and prostate for average-risk individuals, and for lung cancer for those at a higher risk (individuals with a history of smoking). These recommendations are based on several factors, including age, sex, family history, lifestyle, and environmental exposures. USPSTF regularly reviews new scientific evidence and, if needed, revises these screening guidelines. Unfortunately, the panel has not met since March 2025, delaying the issuance of screening guidance for cervical and prostate cancer, with potentially harmful impact on public health.

Colorectal cancer screening outcomes **improved among adults ages 45 to 49** after USPSTF lowered the screening start age to 45.



This pattern indicates increased earlier detection, when treatment is more likely to be curative.

ESW4

Beyond gaps in guidance, many medically underserved population groups face systemic and structural barriers, preventing them from receiving routine screening and/or timely follow-up care. These barriers include lack of health insurance, limited access to quality care, experiences of discrimination, and poor communication with providers.

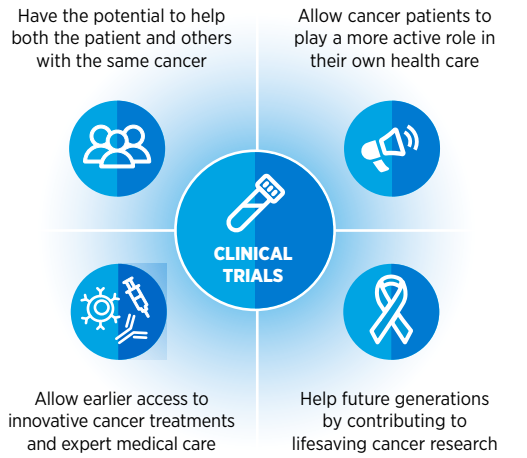
Evidence-based interventions that are helping more people get screened include removing structural barriers to access to routine screening, incorporating patient navigation, and building trust through community-focused approaches. For example, automatically mailed fecal immunochemical test (FIT) kits to screening-eligible individuals are outperforming opt-in approaches for CRC screening. Similarly, patient navigation remains one of the strongest strategies to increase screening uptake. A meta-analysis of 42 clinical trials found that navigation raised breast and cervical screening rates by 13.8 and 15.6 percentage points, respectively. In 2024, CDC formally endorsed patient navigation as a health equity intervention.

Researchers are actively working on improving early detection of cancer, with several new technologies advancing the knowledge of how existing cancers are found and which cancers can be detected early. AI-supported mammography in a trial of over 105,000 women delivered 12 percent fewer interval cancers—cancers found between screenings—and cut radiologists' time evaluating images by 44 percent. Furthermore, FDA cleared two AI-powered lung nodule assessment tools in early 2026. Liquid biopsy, the analysis of blood or other body fluids for tumor-derived material routinely shed during cancer development and treatment, is making it possible to detect cancers early for which there is no screening test available. Genomics-driven, risk-adapted screening is also gaining ground for individuals who are at a higher risk of developing cancer, such as those with a family history of cancer, including **Carolyn Searles** (see p. 94). These advances are exciting but will require long-term studies to ensure that they are beneficial at the population level without causing harm or widening existing cancer disparities.

Progress Across the Clinical Cancer Care Continuum

The dedicated efforts of researchers across the spectrum of cancer science and medicine are driving breakthroughs in

Cancer clinical trials translate medical discoveries into meaningful advances for patients. Clinical trials:



ESW5

clinical care that are improving survival and enhancing quality of life for patients. Clinical trials are a cornerstone of medical research, providing the evidence needed to determine whether new cancer treatments are safe and effective. Advances in our understanding of the molecular drivers of cancer have led to innovative approaches to clinical trial design and execution. For patients with cancer, participating in clinical studies can be life-changing, as reflected in the personal experience of **James Gregory (Greg) Cisneros** (see p. 122).

It is essential that clinical trial participants reflect the diversity of the US population that may use and ultimately benefit from these treatments. Yet, participation in cancer clinical trials remains low, with significant sociodemographic disparities among those enrolled. Addressing these challenges requires collaboration among researchers, clinicians, other health care providers, community partners, and policymakers to remove barriers and promote equitable access to clinical studies.

Surgery, radiotherapy, and chemotherapy are three of the five foundational pillars of cancer treatment. While effective, these therapies can have long-term side effects. Ongoing clinical studies are exploring whether less intensive use of these modalities can provide comparable outcomes for some patients while improving their quality of life. In parallel, more refined uses, such as newer radiotherapy and surgical techniques, molecularly targeted radiotherapeutics, and optimized chemotherapeutic formulations, are being integrated into standard care.

Molecularly targeted therapy and immunotherapy constitute the two most recent pillars of cancer treatment. Fueled by research, these innovative personalized cancer treatments are rapidly moving from the laboratory to the clinic, offering patients safer and more effective options than ever before. Between July 1, 2025, and June 30, 2026, FDA approved 11 new therapeutics for treating various cancer types, one new device for treating pancreatic cancer, and expanded indications for five previously approved therapies to include new cancer types.

Among these approvals are several groundbreaking new treatments. For example, the first molecularly targeted therapy for the rare, aggressive brain tumor, diffuse midline glioma, commonly diagnosed in pediatric and young adult populations, is offering new hope to patients such as **Benjamin (Ben) Stein-Lobovits** (see p. 126). A breakthrough in drug discovery and development was the approval of the first proteolysis-targeting chimera (PROTAC), a molecularly targeted therapeutic that harnesses the cell's protein disposal system to eradicate cancer cells. The treatment was approved for certain patients with breast cancer. Precision medicine for lung cancer continues to advance at a remarkable pace, as illustrated by the stories of **James Gregory (Greg) Cisneros** (see p. 122) and **Sydney Barned, MD** (see p. 26) and the three new FDA approvals of molecularly targeted therapeutics highlighted in the report.

Equally impressive has been the progress in immunotherapies that are reshaping and improving cancer care. FDA expanded the approval of two immunotherapeutics called immune checkpoint inhibitors (ICIs) for the treatment of new cancer types. ICIs work by releasing some of the brakes on the immune system and have been shown to yield remarkable and durable responses. The clinical impact of ICIs continues to expand, with FDA approvals now spanning 23 cancer types and, for the first time, extending to ovarian cancer. Another major advance was the first FDA-approved immunotherapy for high-risk smoldering multiple myeloma, marking a new era of cancer interception by delaying disease progression in patients, including **Jeffrey (Jeff) S. Rubin, MD, PhD** (see p. 142).

While these developments mark significant progress against cancer, much work remains to ensure that all patient populations have access to the latest innovations in cancer treatment including precision medicine. Notably, research shows that disparities in survival rates for many cancers can be drastically reduced when all patients have access to high-quality, guideline-adherent treatments.

Advancing Cancer Survivorship Care

According to NCI, an individual is considered a cancer survivor from the time of diagnosis through the remainder of life. Unprecedented advances in cancer treatment and care have led to more people living longer and fuller lives after a cancer diagnosis. As of January 1, 2025, more than 18.6 million

individuals with a history of cancer were living in the United States, and this number is projected to exceed 22 million by 2035. This represents a substantial increase from the 1970s, when there were an estimated 3 million cancer survivors in the United States.

Cancer survivors comprise a diverse population with a broad range of experiences, health trajectories, and care needs. Some individuals complete their treatment and remain cancer-free, while others live with cancer as a chronic condition that requires ongoing treatment and monitoring. Many survivors experience lasting health challenges as a result of their cancer and its treatment, known as late effects. These include physical, psychosocial, and financial challenges that often persist long after active treatment ends, as highlighted in the personal story of Shauna McLaughlin and her daughter **Madison (Maddie) Bergstrom** (see p. 150). Understanding and addressing the challenges faced by cancer survivors; supporting their long-term health and quality of life; and ensuring equitable access to high-quality care are important priorities in survivorship research.

Certain groups of survivors face unique challenges that require specialized approaches to care. Childhood, adolescent and young adult, and older adult survivors have distinct needs shaped by their age and developmental stage, treatment exposures, underlying health conditions, and social and economic circumstances. Survivorship care for different populations must address not only physical health, but also psychosocial well-being, reproductive health concerns, financial challenges, and transitions in care across the lifespan.

A growing body of evidence demonstrates that lifestyle behaviors, including engaging in regular physical activity, maintaining healthy diet and body weight, and eliminating alcohol and tobacco use, can improve health outcomes and quality of life for cancer survivors. Furthermore, integrating supportive care and routinely collecting patient reported outcomes can improve symptom management, identify unmet needs, and ensure that care reflects survivors' goals and preferences. Patient navigation, survivorship care plans, and care coordination through collaboration among oncology teams, primary care providers, and other health care professionals can help survivors access appropriate services and resources and maintain continuity of care throughout survivorship.

Challenges experienced by patients and survivors of cancer also extend to family members and friends, who often serve as caregivers. In 2025, an estimated 59 million US adults provided ongoing care for adults with complex medical conditions, including over 4 million providing care specifically to a person with cancer. Cancer caregivers play a critical role in helping patients with cancer manage medications, coordinate medical appointments, monitor symptoms, communicate with health care teams, and carry out day-to-day activities. Although caregivers are essential partners in cancer care, their responsibilities can result in substantial emotional and financial strain that adversely affects their quality of life. Proactively identifying and addressing caregiver needs is therefore an important component of comprehensive survivorship care. As the number of cancer survivors continues to grow, advancing research, policies, and clinical practices that support both survivors and caregivers will be critical to improving outcomes for everyone affected by cancer.

Envisioning the Future of Cancer Research

Breakthrough discoveries and technological advances across the fields of medicine have substantially increased our understanding of cancer initiation and progression. This foundational knowledge is driving better strategies to reduce the risk of developing cancer, detect cancer at the earliest possible stage, and treat cancer effectively and more precisely—with fewer long-term side effects.

The extraordinary opportunities to translate our growing understanding of cancer biology into more precise and effective therapies are a source of great optimism for cancer researchers, including **AACR President 2026–2027, Keith T. Flaherty, MD, FAACR** (see p. 168).

Emerging technologies are driving progress against cancer by enabling researchers to investigate tumors with greater precision. Single-cell multi-omics and computational approaches are enabling researchers to map the genetic and functional states of individual cells within tumors, providing new insight into tumor evolution, the TME, and the mechanisms that influence cancer development and treatment resistance. At the same time, organoid systems and three-dimensional bioprinted tumor models are advancing our understanding of the disease by more closely mimicking cancer

Keith T. Flaherty, MD, FAACR

AACR President 2026–2027

"We are entering a remarkable moment in cancer research. Advances in genomics, immunology, and artificial intelligence are helping us better understand the complexity of cancer and opening new opportunities to develop therapies that more precisely match each patient's disease."

biology and accelerating the development of more effective, personalized therapies.

AI is transforming cancer research and patient care by enabling faster, more accurate, and personalized approaches across cancer research and patient care. AI is now being applied to analyze histopathology images more rapidly, identify genomic alterations with great precision, streamline drug development, and support clinical decision-making. Another rapidly advancing technology is liquid biopsy. Liquid biopsy offers a minimally invasive alternative to the traditional tissue biopsy and is being integrated into efforts to enhance early detection, improve diagnosis, inform treatment selection, and monitor disease progression or recurrence.

A wave of innovative new therapies, many still at an investigational stage, will be advancing the frontiers of precision oncology and are poised to transform the future of cancer care. Innovations in drug delivery technologies, such as engineered nanoparticles, are improving the precision of therapeutic delivery, while decades of basic research have paved the way for the next generation of molecularly targeted therapeutics such as those targeting KRAS, one of the most commonly mutated proteins in cancer. These include treatments that target a broader range of KRAS mutations, degrade KRAS proteins, and harness the immune system to attack *KRAS*-driven cancers.

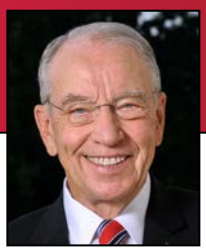
Another exciting area in cancer medicine is the development of vaccines that either prevent cancer in high-risk individuals or treat existing disease by training the immune system to recognize and attack tumor cells, as seen in the experience of **Donna Gustafson** (see p. 176). Researchers are also developing RNA medicines that use programmable RNA molecules to produce therapeutic proteins, silence cancer-promoting genes, and stimulate anticancer immune responses. Rapid advances in RNA chemistry and delivery technologies are expanding the potential of these approaches.

Advancing Cancer Science and Medical Research Through Evidence-based Policies

The progress described throughout this report was not inevitable. It was built over decades through sustained federal investment, scientific discovery, evidence-based policymaking, and bipartisan commitment to medical research. Through NIH, NCI, FDA, CDC, and other federal science and public health agencies, the United States has created a research enterprise capable of turning discoveries into better preventive interventions, earlier detection, safer and more effective treatments, and longer survival for patients with cancer.

The results can be measured in the millions of lives saved and individuals living longer and fuller lives after a cancer diagnosis.

THE HONORABLE
Chuck Grassley
US Senator for Iowa



"Cancer impacts American families across the country, regardless of one's political ideology. That means lawmakers from both sides of the aisle represent Americans battling a cancer diagnosis.

"As a member of the Congressional Biomedical Research Caucus and the Congressional Caucus on the Deadliest Cancers, I work hard to raise public awareness and conduct oversight on federal investments in cancer research to help save lives. Through policymaking and legislative work, I am committed to building bipartisan coalitions that push for robust research, prevention, and treatment options to help cancer patients survive, thrive, and lead healthy, high-quality lives. That includes reducing barriers to care, lowering costs for life-saving drugs, expanding access to experimental treatments, including those being studied in clinical trials such as the one helping my former colleague Senator Ben Sasse, and supporting Right to Try laws, protecting the integrity of medical research, and treating side effects of chemotherapy, such as my bipartisan success to enact the Lymphedema Treatment Act.

"We must also champion expanding access to cancer care in rural America, including my home state of Iowa, which ranks second highest in the United States for new cancer cases. From expanding telehealth services to addressing provider shortages and securing the largest investment in rural health in history with passage of the Rural Health Transformation Fund, advocacy for cancer prevention, treatment, and cures must continue."

They show that progress against cancer does more than change the course of the disease. It changes the course of a life.

In fiscal year (FY) 2026, Congress reaffirmed the nation's bipartisan commitment to medical research by rejecting proposed cuts to NIH and NCI and providing modest funding increases for both agencies. Yet the amount Congress appropriates tells only part of the story. How those funds are administered determines whether laboratories remain stable, studies proceed as planned, and promising ideas have an opportunity to advance public health. When funding is

THE HONORABLE
James Walkinshaw

US Representative for Virginia's 11th District

"Congress has a responsibility to provide stable funding, rigorous oversight, and long-term certainty for our nation's scientific institutions. Scientific research cannot operate on political timelines. Breakthroughs take years of sustained investment, collaboration, and careful review. Staffing disruptions, funding uncertainty, and efforts to weaken our research agencies make it harder to recruit and retain the talented scientists our country depends on. Congress should ensure that agencies like NIH, NCI, and FDA have the resources, personnel, and independence necessary to carry out their missions."

delayed, narrowed, or structured in ways that reduce the number of meritorious grants supported, early-career scientists may lose critical support, clinical trials may open later than planned, and patients may have fewer opportunities to benefit from lifesaving research.

The case for sustaining this investment is economic as well as human. In FY 2025, NIH-supported research generated more than $94 billion in economic activity and supported nearly 391,000 jobs nationwide. Every dollar invested generated approximately $2.57 in economic activity. As other nations expand their investments in medical research and drug development, the United States cannot assume that its leadership will endure.

Funding, however, is only one part of what keeps this system functioning well. The strength of the nation's cancer research and care system also depends on the people, agencies, and infrastructure that move discoveries into patient care. A highly skilled and supported workforce drives scientific innovation. Strong regulatory science and modern, patient-centered clinical trials help FDA deliver safe and effective therapies to patients as quickly as possible. Cancer prevention and screening, including vaccination and tobacco control programs, reduce cancer risk and save lives. Interoperable health information, responsible digital health technologies, and trustworthy AI can also reshape how cancer is studied, detected, treated, and managed across survivorship.

Even the strongest research system falls short if patients cannot benefit from its advances. Too many people still face financial, geographic, and structural barriers to screening, clinical trials, high-quality treatment, and survivorship care.

With policies that expand access and put scientific advances into practice, more people can benefit from cancer prevention and early detection, receive effective treatment, and live longer, healthier lives.

AACR Call to Action

The advances highlighted throughout this report show that the value of a national commitment to medical research is measured not only in scientific discoveries, but in lives improved and saved. That progress now faces a direct threat. The Office of Management and Budget's (OMB) proposed rule, "Regulation for Federal Financial Assistance," would inject political considerations into funding decisions and give federal agencies broader authority to terminate grants, including awards supporting ongoing clinical trials, for reasons unrelated to scientific merit or recipient performance. The Senate's bipartisan action to block the rule through December 11, 2026, is important, but temporary. Congress must extend that protection through final FY 2027 appropriations legislation and provide a robust increase in funding for NIH.

AACR urges elected leaders to take immediate action to:

Sustain the Foundations of Discovery

- **Provide robust and sustained federal investment in medical and cancer research.** Congress should provide at least $51.303 billion for NIH and at least $7.999 billion for NCI in FY 2027 to sustain a broad and competitive research portfolio and fuel continued progress against cancer and other diseases.
- **Ensure that federal research funds are implemented as Congress intended.** Appropriated funds must be awarded in a timely and predictable manner, and NIH must have sufficient staffing and expertise to administer them effectively.
- **Prioritize the cancer research workforce.** Federal policies must give early-career and early-stage investigators the stability to establish independent careers, pursue bold ideas, and build successful research programs.

Protect Scientific Integrity and Independence

- **Stop the proposed OMB rule and preserve scientific merit as the foundation of federal research funding.** Congress must prevent the rule from being finalized or implemented and ensure that funding decisions are guided by rigorous evaluation by scientific experts, not political or ideological considerations.

- **Safeguard the stability of active research awards and clinical trials.** Research grants should not be terminated for reasons unrelated to recipient performance, scientific integrity, or responsible stewardship of federal funds.
- **Protect scientific exchange and responsible international collaboration to maximize innovation.** Researchers must be able to publish and share findings, access scientific literature, participate in conferences, and pursue legitimate international collaborations subject to rigorous, risk-based oversight.

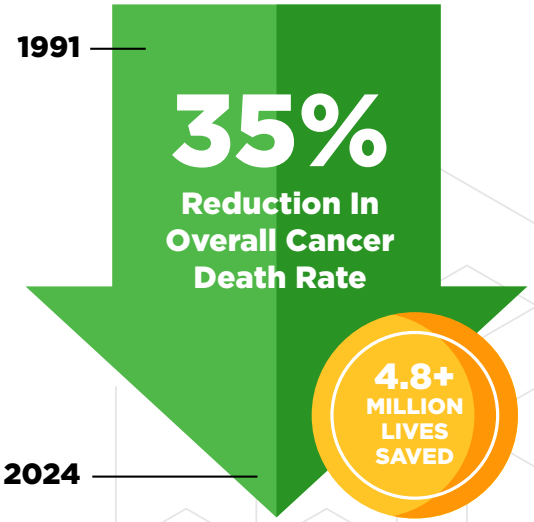
Ensure That Every Patient Benefits From Progress Against Cancer

- **Strengthen FDA's oncology expertise and regulatory science capacity.** The agency must be equipped to support modern, patient-centered clinical trials while maintaining rigorous standards for safety and effectiveness.
- **Sustain evidence-based public health programs that prevent cancer and promote earlier detection.** US public health agencies must have the resources, expertise, and independence needed to support screening, tobacco control, vaccination, and other proven strategies.
- **Modernize the infrastructure that connects research and care.** Policymakers should invest in interoperable data systems, responsible digital health technologies, the oncology workforce, and community-based care infrastructure.
- **Remove barriers to cancer prevention and care.** Policymakers should expand access to screening, clinical trials, treatment, and survivorship care. Rural and medically underserved communities, people with limited insurance coverage, and populations that have historically experienced worse cancer outcomes must be central to these efforts.

Cancer is not partisan. Decisions about which research moves forward must be guided by scientific merit, not political priorities. Congress must protect that principle, sustain robust federal investment, and ensure that the United States continues to lead the world toward a future without cancer.

Scan the QR code
to watch a brief video featuring the survivors in this report.

A Snapshot of Progress



Between July 1, 2025, and June 30, 2026, FDA approved:

- **11** **New anticancer therapeutics**, which are now benefiting patients with various types of cancer
- **5** **Previously approved anticancer therapeutics** for treating new types of cancer
- **1** **New device** for treating pancreatic cancer
- **1** **New at-home self-collection kit** for human papillomavirus (HPV)
- **AI** **Several artificial intelligence (AI)–based tools** to improve early detection and diagnosis of cancers

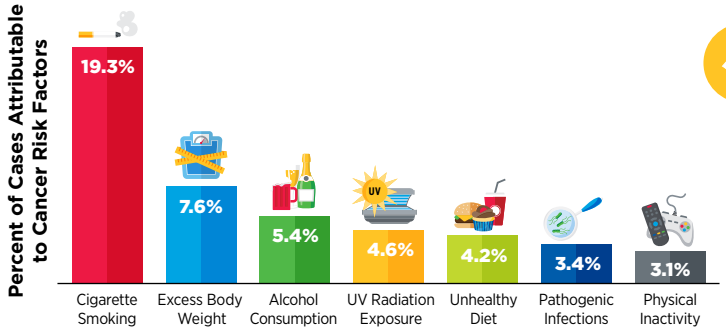
Research continues to advance immunotherapy, leading to:

- The first approval of a therapeutic antibody for patients with high-risk smoldering multiple myeloma, such as **Jeffrey (Jeff) S. Rubin, MD, PhD** (see p. 142).
- The first approval of a chimeric antigen receptor (CAR) T-cell therapy for patients with marginal zone lymphoma, expanding the use of this transformative immunotherapy for a new type of cancer.
- The first approval of an immune checkpoint inhibitor for the treatment of patients with ovarian cancer.

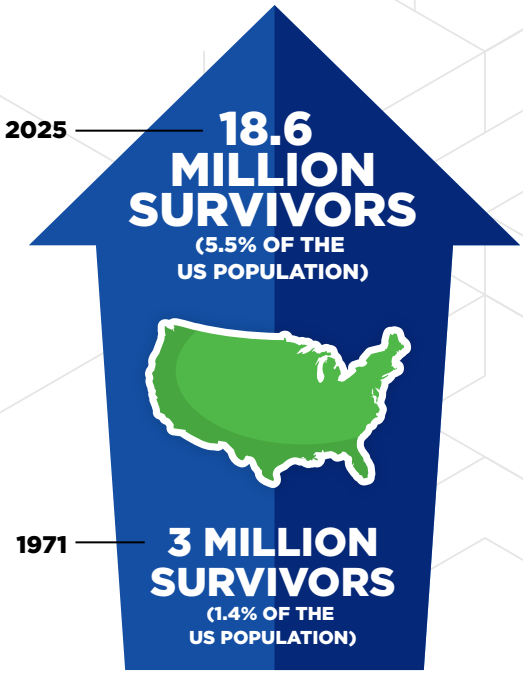
Research continues to power precision medicine, leading to:

- The first ever approval of a proteolysis-targeting chimera, a molecularly targeted therapeutic that harnesses the cell's protein degradation machinery to kill cancer cells, for patients with breast cancer.
- The approval of a novel molecularly targeted therapeutic for an aggressive brain cancer that is bringing new hope to patients, such as **Benjamin (Ben) Stein-Lobovits** (see p. 126).
- Three new molecularly targeted therapeutics for patients with lung cancer, such as **James Gregory (Greg) Cisneros** (see p. 122), whose tumors have certain molecular characteristics.

Approximately 40% of all US cancer cases are attributable to modifiable risk factors such as:



In June 2026, FDA approved the use of bemotrizinol in sunscreens. Bemotrizinol is the first new active ingredient approved by FDA for over-the-counter sunscreens since the late 1990s.



Emerging technologies and next-generation treatments are reshaping the future of cancer research and medicine.

Artificial intelligence enables faster and more efficient approaches to cancer research and clinical care.

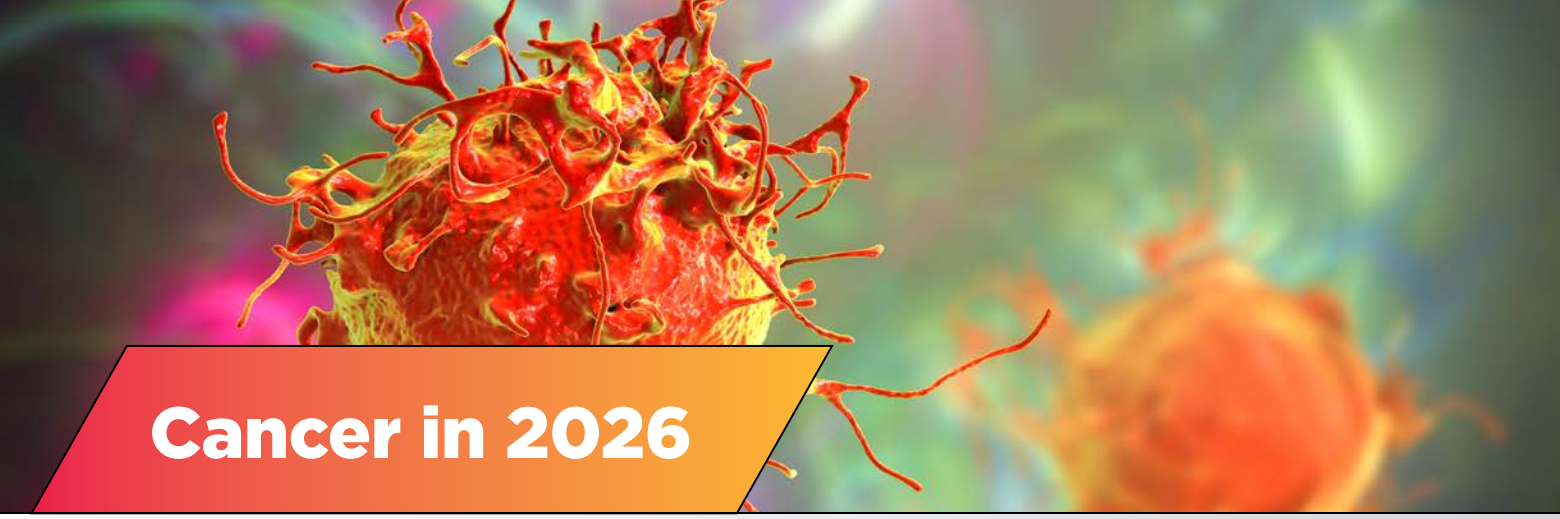
Liquid biopsy enhances early detection and improves treatment and monitoring of disease progression and recurrence.

Cancer vaccines eradicate cancer by activating the immune system, benefiting patients such as **Donna Gustafson** (see p. 176).

RNA medicines treat cancer by programming cells to produce therapeutic proteins or regulate disease-causing genes.

To continue the momentum againt cancer, AACR urges Congress to:

- **PROVIDE** at least $51.303 billion for NIH and $7.999 billion for NCI in fiscal year 2027.
- **ENSURE** appropriated funds reach researchers and support the cancer research workforce.
- **STOP** OMB's proposed rule and protect scientific merit in grantmaking.
- **STRENGTHEN** FDA oncology expertise and regulatory science capacity.
- **SUSTAIN** evidence-based cancer prevention programs.
- **REMOVE** barriers to screening, clinical trials, treatment, and survivorship care.



Cancer in 2026

IN THIS SECTION, YOU WILL LEARN:

- In the United States (US), the overall cancer death rate declined by 35 percent between 1991 and 2024, translating into more than 4.8 million cancer deaths averted.
- The decline in the overall US cancer death rate is largely attributable to reductions in smoking, as well as improvements in early detection and treatment for certain cancers.
- Approximately 18.6 million cancer survivors were living in the United States as of January 1, 2025.
- Substantial inequities in the burden of cancer persist across many segments of the US population and are largely driven by structural and social factors.
- The economic burden of cancer on individuals and the US health care system is projected to increase in the coming decades, underscoring the need for sustained research investment and stronger federal support for medical science and public health.
- Continued progress against cancer will require collaboration among all stakeholders to drive scientific discovery and ensure that advances across the cancer continuum translate into improved outcomes for all populations.

Research: Driving Progress Against Cancer

Research is the cornerstone of progress against the collection of diseases we call cancer. It fuels basic science discoveries, accelerates clinical breakthroughs, and informs public policies designed to improve health outcomes, ultimately saving lives and enhancing quality of life. Advances across basic, clinical, translational, and population sciences, along with technological innovations such as artificial intelligence and machine learning (see **Envisioning the Future of Cancer Research**, p. 166), are fueling new strategies for cancer prevention, early detection, diagnosis, treatment, and survivorship care.

Every scientific innovation and effective policy that drives progress against cancer represents the culmination of a complex process shaped by years of coordinated effort and multidisciplinary collaboration among diverse stakeholders (see **Sidebar 1**, p. 15). Together, these efforts have led to remarkable advances against cancer. Between 1991 and 2024, the age-adjusted overall cancer mortality rate in the United States (US) declined by 35 percent, a reduction that translates into more than 4.8 million cancer deaths averted (1,2). The contribution of treatment advances to declines in cancer mortality has accelerated over the past decade. A recent study estimated that advances in cancer therapies and improved access to care prevented 173,900 cancer deaths among US cancer patients diagnosed between 2010 and 2019 (3).

The steady decline in overall US cancer mortality is largely driven by decreased smoking rates and subsequent declines in lung cancer deaths, a trend that has accelerated in recent years due to advances in early detection and treatment (2). Declines in death rates for colorectal cancer (CRC) and female breast cancer have also played a key role in reducing overall US cancer mortality. From 1989 to 2024, the US female breast cancer mortality rate declined by 44 percent, a reduction that translates into an estimated 546,000 fewer breast cancer deaths due to advances in screening mammography and personalized treatments (2,4). Similarly, the death rate for CRC declined by nearly 50 percent between 1990 and 2024 (1). However, this progress has been largely limited to older

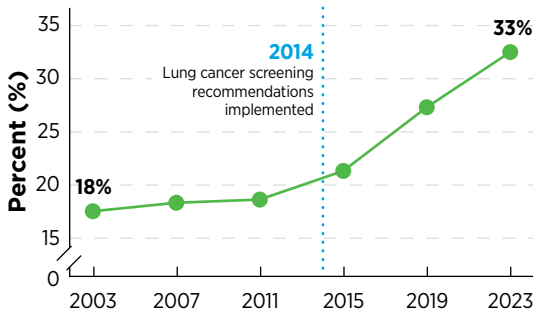
SIDEBAR 1

The Medical Research Community: Driving Progress Together

Progress against cancer can be accelerated when all stakeholders committed to reducing the burden of cancer work together. Strengthening collaboration across the medical research ecosystem can drive scientific discovery, foster innovation, and improve patient outcomes. Key stakeholders in medical research include:

adults, as mortality rates for early-onset CRC, defined as CRC diagnosed in individuals aged 18 to 49 years, have increased by approximately 1 percent per year since 2004, and CRC is now the leading cause of cancer death in this age group (5,6). Mortality rates have also declined over the past decade for melanoma, leukemia, and cancers of the kidney and prostate, despite stable or increasing incidence rates, further underscoring the impact of advances in treatment (1,2).

US Lung Cancer Cases Diagnosed at Early Stage (2003–2023)



Sources: (7,8). W1

Breakthroughs across the spectrum of cancer science and medicine have led to unprecedented progress against cancers once considered intractable. For example, groundbreaking basic research conducted during the 1960s through 1980s identified the mechanistic underpinnings of chronic myeloid leukemia (CML), a cancer of the blood and bone marrow, laying the foundation for the development of new therapies that have dramatically improved outcomes for patients with the disease (see **Generating Knowledge Through Basic Research**, p. 31) (9). As a result, the 5-year relative survival rate for CML has more than tripled, from 22 percent in the mid-1970s to 71 percent among individuals diagnosed during 2016–2022 (1,2). More recently, the development of immunotherapies has markedly improved outcomes for patients with multiple myeloma, increasing the 5-year relative survival rate from 32 percent in the mid-1990s to 64 percent during 2016–2022 (1,2).

Other historically lethal cancers have also experienced meaningful, though more modest, improvements in survival. For example, the 5-year relative survival rate for liver cancer has increased three-fold, from 7 percent in the mid-1990s to 22 percent for individuals diagnosed during 2016–2022 (1,2,10).

Average Annual Decline in US Death Rates for Selected Blood Cancers (2015–2024)

Hodgkin Lymphoma	Leukemia	Multiple Myeloma	Non-Hodgkin Lymphoma
▼3.2%	▼3.0%	▼2.5%	▼2.4%

Source: (1). W2

These gains are linked to advances in systemic therapies, which, although often not curative in advanced stages, can prolong survival (11).

Research-driven advances have also improved survival outcomes for patients with metastatic, or distant-stage, cancer. For all cancers combined, the 5-year relative survival rate for distant-stage disease increased from 17 percent in the mid-1990s to 36 percent during 2016–2022 (2,12). These improvements were especially notable for distant-stage melanoma, as well as distant-stage lung and rectal cancers, for which 5-year relative survival has more than doubled since the mid-1990s.

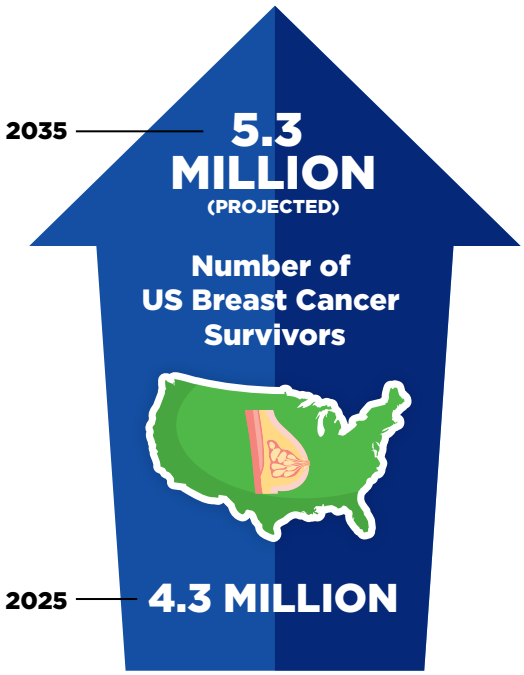
Survival trends are also shaped by changes in the prevalence of cancer risk factors and tumor subtypes over time. For example, the 5-year relative survival rate for people diagnosed with cancers of the oral cavity and pharynx increased from 58 percent in the mid-1990s to nearly 70 percent in recent years (1,2). This improvement is driven, in part, by reductions in smoking-related cancers and an increase in human papillomavirus (HPV)–associated cancers, which tend to have a more favorable prognosis than HPV-negative cancers. Over the past three decades, the proportion of HPV-related oral cavity cancers—including cancers of the tongue, tonsil, and oropharynx—has increased from 37 percent to 58 percent (2).

Progress Against Metastatic Cancer

The 5-year relative survival rate for metastatic cancers has improved substantially since the mid-1990s.

	1995–1997		2016–2022
All cancers combined	17%	→	36%
Lung	2%	→	10%
Melanoma	16%	→	34%
Rectal	8%	→	19%
Stomach	3%	→	8%

Sources: (2,12). W3



Source: (13).

W4

Major advances across the clinical cancer care continuum from July 1, 2025, to June 30, 2026, include 11 new anticancer therapeutics that were approved for use by the US Food and Drug Administration (FDA). During this period, FDA also approved new uses for five previously approved anticancer therapeutics, one new device for treating pancreatic cancer, and a device for at-home sample collection for cervical cancer screening. FDA also approved a number of artificial intelligence–powered devices and software for aiding cancer risk prediction, diagnosis, and early detection.

Collectively, advances such as these and those described in past editions of this annual report are helping to increase the number of children and adults who live longer and fuller lives after a cancer diagnosis. The 5-year relative survival rate for all cancers combined has increased from 49 percent among individuals diagnosed in the mid-1970s to a milestone 71 percent among those diagnosed during 2016–2022 (see **Figure 1**, p. 18) (1). Similar progress has been made among US children (ages 0 to 14) and adolescents (ages 15 to 19) diagnosed with cancer, whose 5-year relative survival rate for all cancers combined improved from 58 percent in the mid-1970s to 86 percent during 2016–2022 in children and from 68 percent to 88 percent in adolescents (12,13). As of January 1, 2025, there were 18.6 million people living in the United States with a history of cancer, and this number is projected to exceed 22 million by 2035. As the population of cancer survivors continues to grow, prioritizing research that addresses their evolving needs must remain a critical focus for US medicine and public health (see **Advancing Cancer Survivorship Care**, p. 144).

Cancer: An Ongoing Challenge

While substantial progress has been made against cancer, the disease continues to be an enormous public health challenge in the United States and around the world. In 2026, an estimated 2,114,850 new cancer cases will be diagnosed, and 626,140 people will die from the disease in the United States (see **Table 1**, p. 19). However, the burden of cancer is not distributed equally, as many population groups in the United States continue to experience disproportionately high rates of cancer incidence and mortality.

Inequities in the Burden of Cancer in the United States

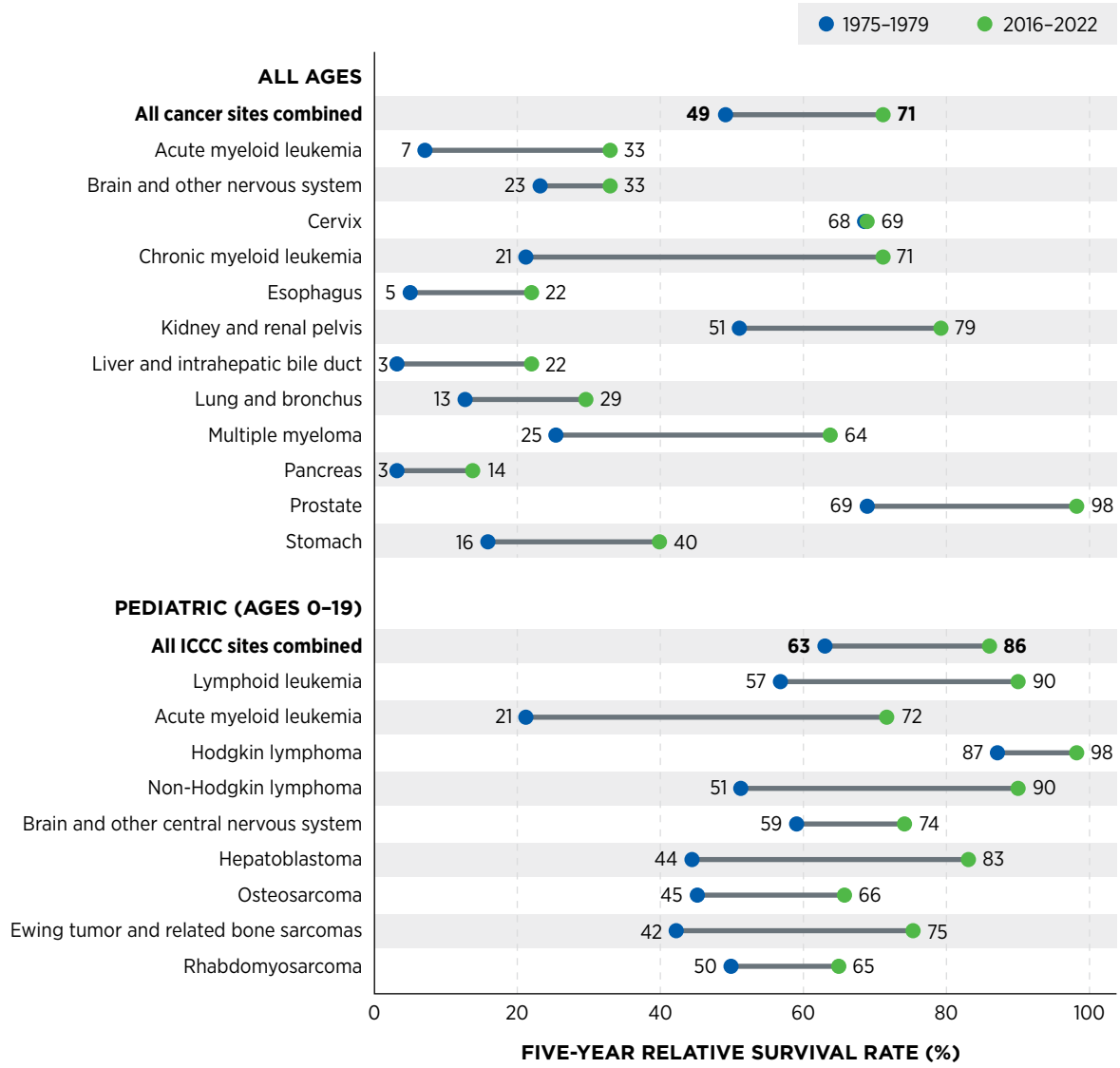
Advances in cancer prevention, early detection, treatment, and survivorship care have led to substantial improvements in cancer outcomes in the United States over the past several decades. However, these advances have not benefited everyone equally, and certain segments of the US population continue to shoulder a disproportionate burden of cancer. Cancer disparities remain one of the most pressing public health challenges in the United States. A long history of racism, segregation, and discrimination against marginalized population groups has resulted in structural inequities and societal injustices that continue to drive and perpetuate US cancer disparities. Understanding and addressing the underlying drivers of cancer disparities is essential to ensuring that advances against cancer benefit all populations.

The National Cancer Institute (NCI) defines cancer disparities as adverse differences between certain population groups in cancer-related measures, including the number of new cases, the number of cancer deaths, screening rates, stage at diagnosis, cancer-related health complications, and survivorship and quality of life after treatment (see **Sidebar 2**, p. 20).

The *AACR Cancer Disparities Progress Report 2026* highlights the disproportionate burden of cancer among US racial and ethnic minority groups and other medically underserved populations (see **Sidebar 3**, p. 21) (16). For example, overall cancer incidence rates during 2019–2023 were highest among Black men and American Indian or Alaska Native (AIAN) women, compared to other racial and ethnic groups (1). Similarly, Black individuals had the highest overall cancer mortality rate during 2020–2024, followed by AIAN individuals. Hispanic, Asian, and Native Hawaiian or Pacific Islander (NHPI) populations experience disproportionate burdens of infection-related cancers, such as liver and stomach cancers. Other concerning trends include increasing rates of early-onset CRC among AIAN populations as well as the rising incidence of lung cancer in Asian women who have never smoked (6,17,18). Additionally, during 2016–2022, patients with cancer from

FIGURE 1

Decades of Progress in Cancer Survival



ICCC, International Classification of Childhood Cancers.

Five-year relative survival rates for all cancers combined and for many major cancer types improved substantially in the United States between 1975–1979 and 2016–2022. Improvements varied by cancer type, with some of the largest absolute gains observed for chronic myeloid leukemia, multiple myeloma, prostate cancer, kidney cancer, and pediatric acute myeloid leukemia, reflecting decades of progress in prevention, early detection, treatment, and survivorship care. However, progress has been uneven, and some cancers continue to have relatively low 5-year survival rates.

Sources: (12,14).

all racial and ethnic minority groups had lower 5-year relative survival rates (61.5 percent to 68.9 percent) than White individuals (71.4 percent) (1).

Research on the science of cancer disparities is revealing significant differences in cancer incidence and mortality across subpopulations within broad racial and ethnic categories,

TABLE 1

Estimated Burden of Common Cancer Types in the United States (2026)

	New Cases	Deaths
All cancers combined	**2,114,850**	**626,140**
Prostate	333,830	36,320
Breast	321,910	42,140
Lung and bronchus	229,410	124,990
Colorectal	158,850	55,230
Melanoma of the skin	112,000	8,510
Bladder	84,530	17,870
Kidney and renal pelvis	80,450	15,160
Non-Hodgkin lymphoma	79,320	19,970
Uterine	68,270	14,450
Pancreatic	67,530	52,740
Thyroid	45,240	2,320
Liver and intrahepatic bile duct	42,340	30,980
Multiple myeloma	36,000	10,850

Source: (15).

underscoring the need for disaggregated data. This issue is particularly relevant for Asian and NHPI populations, whose cancer statistics are often reported in aggregate, potentially masking substantial disparities between NHPI and Asian populations as well as important differences among Asian subgroups. For example, according to a recent study, Southeast Asian and NHPI individuals had 17 percent and 34 percent higher risks of death from non-Hodgkin lymphoma, respectively, compared to East Asian individuals, whereas South Asian individuals had a 16 percent lower risk (25). These findings highlight the importance of collecting and reporting disaggregated data to better understand and address cancer disparities within and among distinct population groups and to guide more equitable cancer control efforts.

In addition to racial and ethnic minority groups, cancer disparities persist across many segments of the US population, including rural residents, people living in persistent-poverty areas, and members of sexual and gender minority (SGM) communities. For example, overall cancer incidence (2019–2023) and mortality (2020–2024) rates were approximately 6 percent and 18 percent higher, respectively, among rural residents than among those living in urban areas (1). Overall cancer death rates have also declined more slowly in rural counties, further widening disparities between rural and urban populations (26,27).

Individuals living in persistent-poverty areas also experience worse outcomes across the cancer continuum than those in non–persistent-poverty areas, including higher incidence, more advanced stage at diagnosis, and higher mortality across multiple cancer types (28,29).

Additionally, SGM populations experience a disproportionate burden of cancers associated with HPV and human immunodeficiency virus (HIV), including Kaposi sarcoma, anal cancer, and testicular cancer (30). However, population-level data on cancer incidence and mortality among SGM populations remain limited, hindering efforts to fully understand and address cancer disparities in this population.

Researchers have developed several frameworks to understand and address the factors that shape health outcomes and contribute to inequities in cancer prevention, diagnosis, treatment, and survival (31-34). These frameworks consistently emphasize that health outcomes are shaped by a complex interplay of biological, behavioral, social, environmental, and health care system factors operating across multiple levels of influence. Increasing attention has focused on social drivers of health (SDOH) as important contributors to cancer disparities. NCI defines SDOH, also known as social determinants of health, as the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and get older that can affect their health, well-being, and quality of life. SDOH include factors such as socioeconomic status; housing; transportation; and access to healthy food, clean air and water, and health care services (see **Figure 2**, p. 22).

It is important to recognize that individuals with intersecting identities, such as those from racial and ethnic minority groups living in socioeconomically disadvantaged communities, often face compounding barriers to high-quality cancer care that can contribute to poorer outcomes across the cancer continuum. For example, a study examining differences in 5-year cancer survival by race and urbanicity of county of residence found that survival was generally lower among Black individuals than among White individuals and among individuals living in rural areas compared to those living in urban areas. Notably, Black individuals residing in rural areas experienced the lowest 5-year survival for all cancers combined and for several individual cancer types (35).

Inadequate access to quality health care is a major social driver of cancer disparities. In the United States, health insurance coverage is a key determinant of access to care across the cancer continuum, including cancer prevention, screening, treatment, and survivorship care services. National data show that individuals without insurance are less likely to undergo recommended cancer screening (36,37). Insurance-related

SIDEBAR 2

US Population Groups That Experience Cancer Disparities

NCI defines cancer disparities as adverse differences in cancer-related measures, such as the number of new cases and deaths, screening rates, stage at diagnosis, cancer-related health complications, and quality of life after cancer treatment, that disproportionately affect certain population groups, including:

Individuals belonging to certain ancestral, racial, or ethnic minority populations

Individuals who lack or have inadequate health insurance coverage

Individuals with disabilities

Individuals who are incarcerated

Older adults

Residents in certain geographic locations, including rural areas and communities experiencing poverty

Individuals of low socioeconomic status, including low educational attainment

Individuals belonging to sexual and gender minority communities

Adolescents and young adults

Immigrants, refugees, or asylum seekers

Citizens of sovereign Native Nations

barriers also affect clinical trial enrollment and access to cancer treatment after diagnosis. For example, patients with Medicaid or no insurance are less likely than privately insured patients to enroll in cancer clinical trials (see **Clinical Research**, p. 99) (38,39). Patients without private insurance are also less likely to receive biomarker testing and newer therapies such as immunotherapy (40-42). These insurance-related disparities also extend to the quality and timeliness of cancer care. Across multiple cancer types, studies show that patients without private insurance are less likely to receive guideline-concordant care and more likely to experience delays in treatment initiation, both of which are associated with worse cancer outcomes (43-47).

The persistence of cancer disparities across multiple segments of the US population underscores the need for concerted efforts to understand and address the complex, multilevel factors that shape cancer outcomes. Achieving health equity will require sustained progress across the full spectrum of cancer science and medicine, including basic and translational research that incorporates biospecimens and data from diverse populations; clinical studies that include participants from all sociodemographic backgrounds; and health care delivery and implementation research that reflects the needs, priorities, and lived experiences of populations disproportionately affected by cancer. These efforts are critical to ensuring that advances in cancer prevention, early detection, treatment, and survivorship care translate into improved outcomes for all populations.

Variable Progress Against Different Types of Cancer and Stages of Diagnosis

Despite substantial progress in reducing the overall cancer burden in the United States, advances have been uneven across cancer types and stages. This disparity is reflected in wide variations in 5-year survival rates, which depend strongly on both the cancer type and the stage at diagnosis.

For example, between 2016 and 2022, the overall 5-year relative survival rate was 13.7 percent for pancreatic cancer and 6.6 percent for glioblastoma multiforme, an aggressive form of

SIDEBAR 3

Cancer Disparities in the United States

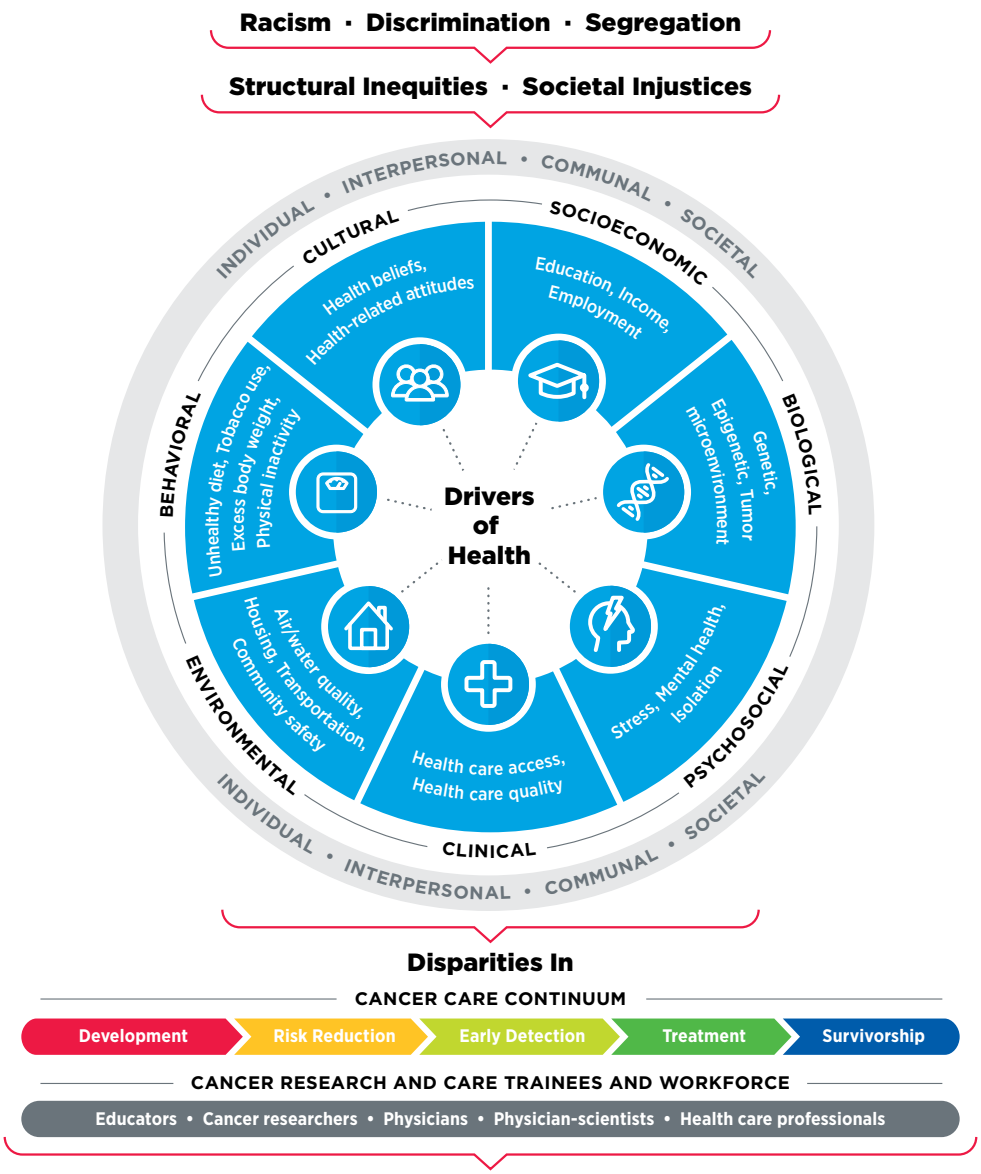
Many segments of the US population shoulder a disproportionate burden of cancer. Selected examples of disparate cancer incidence and outcomes from recent studies are provided here. Disparities in other aspects of cancer care are highlighted in relevant sections throughout this report. An in-depth discussion of cancer disparities and recent progress in addressing these inequities, as well as a call to action, is detailed in the *AACR Cancer Disparities Progress Report 2026* (16).

13% and 9% higher	From 2020 to 2024, overall cancer mortality rates were 13 percent higher among Black men than White men, despite only a 3 percent higher incidence rate, and 9 percent higher among Black women, despite a 10 percent lower incidence rate (1).
LARGEST increases	Between 2011 and 2020, Hispanic individuals experienced the largest increases in early-onset colorectal cancer (CRC) incidence, with annual increases of 4.7 percent among women and 3.5 percent among men, compared to 2.1 percent and 2.7 percent, respectively, among White women and men (19).
20% higher	A study of adolescent and young adult cancer patients across the 10 deadliest cancer types found that Asian individuals had 20 percent higher odds of late-stage diagnosis, yet a 10 percent lower risk of death compared to White individuals (20).
2-fold higher	From 2019 to 2023, incidence rates were about two-fold higher among American Indian or Alaska Native populations than among White populations for cancers of the gallbladder, liver, and stomach, and 40 percent to 50 percent higher for cancers of the colorectum, cervix, and kidney (21,22).
65% and 2-fold higher	Asian or Pacific Islander individuals have a 65 percent higher incidence of stomach cancer and a two-fold higher mortality from the disease compared to White individuals (21,22).
37% and 3-fold higher	Gay and lesbian individuals had a 37 percent higher prevalence of non-melanoma skin cancer compared to heterosexual individuals. Disparities were substantially larger among racial and ethnic minority populations, among whom gay and lesbian individuals had more than three-fold higher prevalence than their heterosexual counterparts (23).
37%, 26% and 17% higher	Incidence rates during 2019–2023 were 37 percent higher for lung cancer, 26 percent higher for cervical cancer, and 17 percent higher for CRC in nonmetropolitan areas compared to large metropolitan areas (1).
26% higher	Children diagnosed with cancer who reside in persistent-poverty areas had a 26 percent higher risk of death within 3 months of diagnosis compared to those living in non–persistent-poverty areas (24).

brain cancer. These figures stand in stark contrast to 91.9 percent for breast cancer and 98.2 percent for prostate cancer (12). However, these overall estimates obscure important stage-specific differences. Among individuals diagnosed with localized disease—cancer confined to the breast or prostate—the 5-year relative survival rate approaches 100 percent. In

FIGURE 2

Drivers of Cancer Disparities in the United States



Complex and interrelated structural and social factors, stemming from a long history of racism and discrimination, drive cancer disparities. These factors include social drivers of health (SDOH) as well as biological factors, mental health, and modifiable risk factors. NCI defines SDOH, sometimes also called social determinants of health, as the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and age that can affect their physical and mental health, well-being, and quality of life. In the United States, historical racism and contemporary injustices have perpetuated and exacerbated systemic inequities, resulting in adverse differences in SDOH for racial and ethnic minority groups and other medically underserved populations. The circle in the figure depicts key drivers of health and how they interconnect at societal, communal, and individual levels. Selected examples of the multilevel factors that make up drivers of health are highlighted. Collectively, these factors impact every stage of the cancer continuum, leading to worse health outcomes for affected individuals.

contrast, those diagnosed with distant or metastatic disease—cancer that has spread to other organs—have markedly lower 5-year survival rates of 33.8 percent for breast cancer and 40.1 percent for prostate cancer (12). These patterns underscore the critical importance of early detection and diagnosis.

Despite these advances, substantial challenges remain for cancers with persistently high mortality. Lung cancer is the third most commonly diagnosed cancer in the United States and remains the leading cause of cancer-related death. Although the lung cancer mortality rate has declined by more than half since 1990 (from 58.8 to 27.9 deaths per 100,000 individuals), it remains higher than that of any other cancer (1). This burden is partly attributable to late-stage diagnosis, as 46.5 percent of lung cancers are diagnosed at advanced stages, compared to 6.1 percent for breast cancer. Low screening uptake also contributes to this disparity. Among cancers with recommended screening, lung cancer has the lowest participation rate, with only 13 percent of eligible individuals reporting a low-dose computed tomography screening test in the past year, compared to 80 percent for breast cancer (see **Cancer Screening for Early Detection**, p. 82) (36). Differences in screening uptake contribute to later-stage diagnosis and higher mortality.

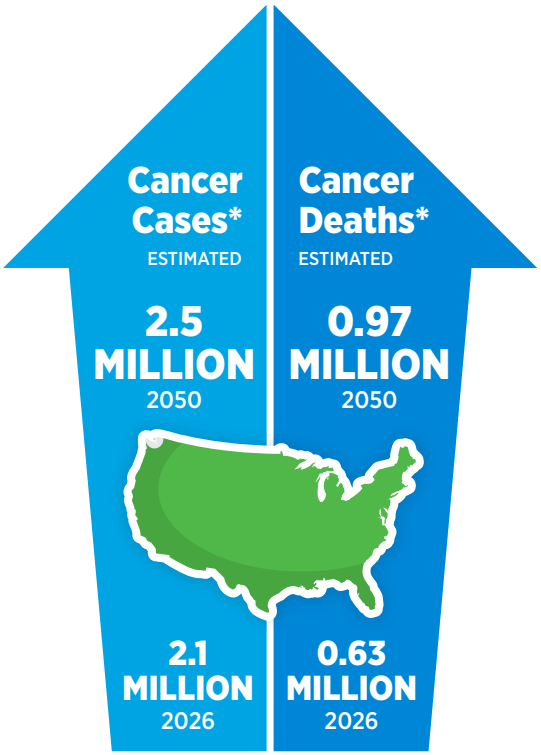
However, disparities in cancer outcomes are not limited to stage at diagnosis. Survival also varies dramatically across cancer types, reflecting differences in disease biology and treatment advances. For example, substantial advances in the treatment of pediatric acute lymphoblastic leukemia have increased 5-year survival to more than 90 percent, whereas diffuse midline glioma—a rare, aggressive brain tumor with limited treatment options—remains among the deadliest pediatric cancers, with a 3 percent 5-year survival rate (12,48).

These stark differences underscore that the advances in cancer research, prevention, early detection, and treatment have not been realized equally across all cancer types, highlighting the need for continued innovation and targeted efforts to improve outcomes for cancers with consistently poor outcomes.

The Growing Population Burden of Cancer

The burden of cancer as a public health issue is expected to grow substantially in the coming decades unless more effective approaches to prevention, early detection, and treatment are put in place. In the United States, the annual number of newly diagnosed cancer cases, excluding non-melanoma skin cancer, is projected to surpass 2.5 million by 2050—representing a 19 percent increase from the estimated 2.1 million cases expected in 2026 (2,49).

A key factor driving this increase is the aging population, as the likelihood of developing cancer rises markedly with age.



* Excluding non-melanoma skin cancer.
Sources: (2,49).

W5

Currently, about 60 percent of all cancer diagnoses occur among individuals age 65 and older (2). By 2050, this age group is expected to grow to more than 82 million people, accounting for approximately 23 percent of the US population. This reflects nearly a 50 percent increase from 2022, when there were about 58 million older adults, making up roughly 17 percent of the population (50). Interestingly, the proportion of cancer cases occurring in adults age 65 and older has remained relatively stable over time, changing only from 61 percent in 1995 to 60 percent in 2022 (2).

An increase in exposure to several modifiable risk factors may also contribute to the rising number of cancer cases in the United States. These include the high prevalence of excess body weight, low levels of physical activity, alcohol use, environmental exposures, and ongoing tobacco use (see **Reducing the Risk of Cancer Development**, p. 55). Although smoking rates have declined markedly since the 1970s, about 12.6 percent of US adults still use combustible tobacco products, such as cigarettes or cigars (51).

Cigarette smoking remains the leading cause of lung cancer. However, the frequency of lung cancer diagnosed in individuals who have never smoked is rising. Globally, an estimated 15 percent to 20 percent of lung cancer cases occur in people with no history of smoking (52). Recent studies show that lung cancer in never-smokers differs from smoking-related lung cancer in both tumor characteristics and disease patterns

Rise in the Incidence of Early-onset Gastrointestinal Cancers (2001–2021)

SITE	PERCENT INCREASE
Intrahepatic bile duct	6.24%
Small intestine	3.19%
Colon and rectum	1.65%
Pancreas	1.52%
Stomach	1.20%

Source: (54).

W6

(52,53). These cancers are most often adenocarcinomas, which originate in mucus-producing cells. Lung cancer in never-smokers also occurs more frequently in women, in individuals of Asian ancestry, and often contain specific genetic alterations that can be treated with molecularly targeted therapeutics, as was the case with **Sydney Barned, MD** (see p. 26) (52).

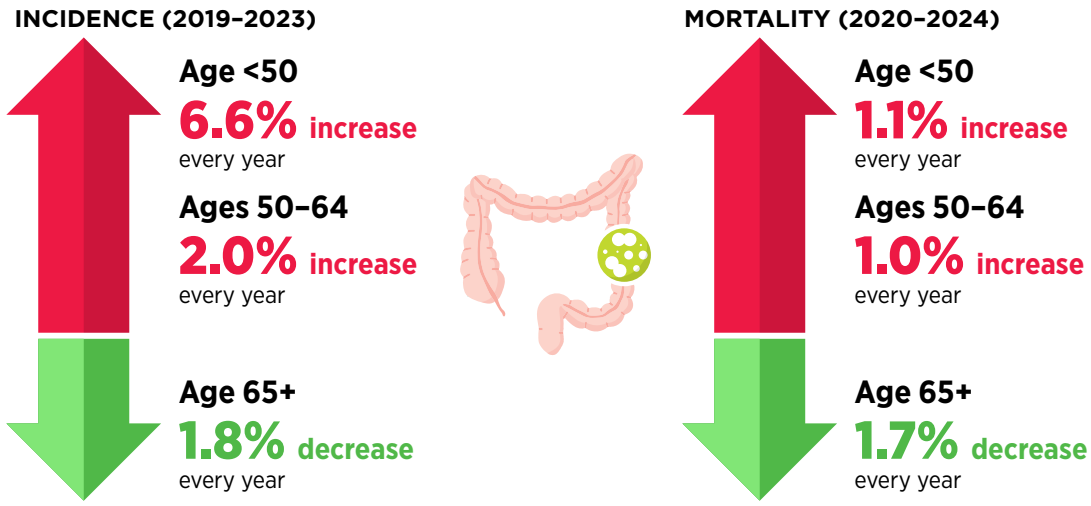
As the number of lung cancers continues to rise in individuals who have never smoked, there is critical need to identify unique risk factors, conduct in-depth characterization of the disease, and develop evidence-based strategies for early detection and treatment to reduce the burden of lung cancer in patients without a history of smoking.

Another rising concern among public health experts is the steadily increasing incidence of certain cancer types among individuals ages 18 to 49, a phenomenon referred to as early-onset cancer. Notably, this age group is the only one to have experienced a consistent increase in overall cancer incidence in the United States between 1995 and 2021. Globally, cancer incidence among individuals under the age of 50 increased by nearly 80 percent between 1990 and 2019 (55). This trend is reflected in patterns across a subset of cancers. Between 2010 and 2019, incidence rates rose for 14 cancer types among US individuals ages 15 to 49, including melanoma; certain lymphomas; and cancers of the cervix, colon, breast, pancreas, stomach, testicles, and uterus (56).

In the United States, these rising rates also reveal notable sex disparities. Cancer incidence among individuals younger than 50 years is higher in women than in men, and this gap has widened over time. In 2023, the incidence of new cancers in this age group was 78 percent higher in females than in males (149.4 vs. 83.9 per 100,000 individuals), compared to a 55 percent difference in 2003 (118.1 vs. 76.2 per 100,000 individuals) (12).

Certain cancer types have contributed disproportionately to the increase in early-onset disease. In particular, the incidence of early-onset gastrointestinal cancers, including cancers of the colorectum, stomach, and esophagus has risen substantially in

Burden of Colorectal Cancer in the United States



Source: (1).

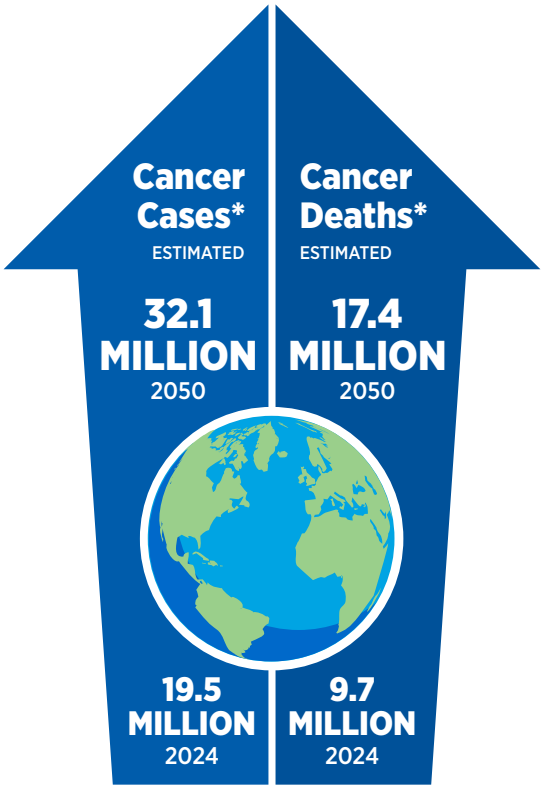
W7

the United States in recent decades (57). These increases are thought to be driven in part by changes in population-level risk factors, including rising obesity rates, more sedentary lifestyles, greater exposure to environmental pollutants, and shifts in dietary patterns (58).

In response to these concerning trends, efforts to promote earlier detection and prevention have intensified. The US Preventive Services Task Force (USPSTF) has updated its screening recommendations, lowering the starting age for colorectal and breast cancer screening to 45 and 40 years, respectively, from the previous benchmark of 50 years. In parallel, researchers are evaluating emerging strategies—such as expanded genetic testing and targeted risk-based approaches—to improve prevention and early detection of CRC in younger populations (59,60).

The Global Burden of Cancer

Globally, cancer remains a leading cause of morbidity and mortality. In 2024, excluding non-melanoma skin cancers, there were an estimated 19.5 million new cancer cases and 9.7 million cancer-related deaths worldwide, with 50.7 percent of incident cases and 56.5 percent of cancer deaths occurring in Asia (61). Given that approximately 60 percent of the world's population resides in Asia, these figures reflect, in part, the region's large population base. The cancers contributing to the greatest number of new cases were lung, female breast, colorectal, prostate, and stomach cancers, accounting for 12.8 percent, 11.8 percent, 9.9 percent, 7.5 percent, and 4.7 percent of all cases, respectively. Lung cancer was also the leading cause of cancer-related death, accounting for 19.1 percent of all cancer deaths, followed by colorectal (9.4 percent), liver (7.5 percent), female breast (7.1 percent), and stomach (6.6 percent) cancers (61).



* Excluding non-melanoma skin cancer.
Source: (49).

W8

Human Development Index (HDI) for Classification of Countries

The HDI is a composite measure of human development that summarizes average achievement in three key dimensions:

- A long and healthy life;
- Access to knowledge; and
- A decent standard of living.

Specifically, these dimensions are measured using life expectancy at birth, educational attainment, and gross national income (GNI) per capita. HDI categories provide a standardized way to compare human development across countries and over time, reflecting health, education, and economic well-being.

Based on a country's overall HDI score, countries are classified into four categories of human development:

VERY HIGH	0.800 and above
HIGH	0.700–0.799
MEDIUM	0.550–0.699
LOW	below 0.550

Source: (63).

W9

To better understand differences in cancer burden across countries, researchers often use the Human Development Index (HDI) or the World Bank classification of countries. The HDI is a measure of a country's overall level of development based on three key areas: health, education, and standard of living—not income alone. Health is measured by

continued on page 28

Sydney Barned, MD
AGE: 43 / ANNAPOLIS, MARYLAND

Thriving Nearly a Decade After a Stage IV Lung Cancer Diagnosis, Thanks to Precision Medicine

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In 2017, almost a year after moving from Jamaica to the United States to begin her medical residency in Washington, DC, Dr. Sydney Barned was focused on her career as a physician. At 33 years old, Sydney was a lifelong athlete who trained in ballet, swam, and ran track, and had never smoked. The last thing on her mind was a diagnosis of cancer.

Sydney's symptoms began with persistent wheezing during the first few months of residency. She assumed that her symptoms were related to a lingering respiratory problem from walking pneumonia she had earlier in the year. After her pulmonologist ruled out asthma, a chest X-ray revealed an abnormality in her lung. As a physician, Sydney felt something wasn't right and requested a follow-up CT scan. The scan showed a mass pressing on her airway; additional testing confirmed a diagnosis of non–small cell lung cancer.

"The irony of my diagnosis is that I used to lecture my friends about smoking as a teenager," Sydney recalled. "I was the one who scolded people about lung cancer, and then I was the one diagnosed with it." Although smoking remains the leading risk factor for lung cancer, the disease is increasingly being diagnosed in people who have never smoked, particularly in younger women.

Initially, physicians thought that Sydney's cancer was stage I and potentially curable with surgery. A follow-up procedure revealed cancer in her lymph nodes, upgrading her diagnosis to stage III, and a subsequent biopsy of the lining surrounding her lung confirmed stage IV disease. Molecular testing of her tumor identified an *ALK* gene rearrangement, a genetic alteration that produces a cancer-driving abnormal protein and could be treated with a molecularly targeted therapy designed to inhibit its activity.

Within months of starting treatment with a first-generation ALK inhibitor, Sydney's wheezing disappeared. She completed her residency while serving as a chief resident, and began working full time as a physician. She married her longtime partner just 2 weeks after her diagnosis. She resumed traveling, exercising, and making time to spend with family and friends. While the first-generation ALK inhibitor, on average, controls the disease for less than a year, Sydney responded very well to the drug and her cancer remained well controlled for more than 5 years.

Sydney underwent routine CT scans every 3 months and brain MRI scans every 6 months to monitor for signs of disease progression. In 2022, the scans detected 3 small brain metastases. Fortunately, years of advances in cancer research had already produced a newer generation of ALK-targeted therapies that could better cross the blood–brain barrier, a protective membrane that keeps most drugs from entering the brain. Sydney started treatment with a second-generation ALK inhibitor, and her 3-month follow-up scan showed her disease had stabilized, and the brain metastases disappeared.

Nearly a decade after her lung cancer diagnosis, Sydney's disease remains well controlled with ALK-targeted therapy alone. "In more than 9 years of living with stage IV lung cancer, I've only taken pills," Sydney said. "I haven't needed chemotherapy, radiation, or surgery."

Today, Sydney is a practicing physician, caring for hospitalized patients, including many with cancer. Sydney has experienced cancer from both sides of the stethoscope. That perspective has shaped how she treats her own patients. She encourages them to speak openly about symptoms and treatment side effects so they can receive the care they need.

Sydney's experience has also made her a passionate advocate for lung cancer awareness. "Anyone with lungs can get lung cancer," she said. "I find that most people still are very unaware of that." Sydney hopes her story will help dispel the misconception that lung cancer is exclusively a disease of people who smoke. "When I was diagnosed, I felt like a unicorn," she added. "I was the youngest person in the room most of the time. Now, unfortunately, that's not the case." Sydney would like to see more research into what is driving this shift. "We're getting more and more non-smokers who are being diagnosed with lung cancer," she said. "We need research into the other risk factors for lung cancer so we can figure out what to do to slow this down."

Her message for policymakers is direct. The therapies that transformed her prognosis exist because of decades of investment in research. "I wouldn't be here if it wasn't for the research that was done over a decade ago," Sydney said. "I was diagnosed at 33 and now I'm 43. Lung cancer research has given me more years with my family, my friends, and my patients. Research funding is necessary because it gives people like me the chance to keep living."

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

life expectancy at birth, education by years of schooling, and standard of living by gross national income per person (62). These indicators are combined into a single score that groups countries into different HDI levels. In contrast, the World Bank classification groups countries solely by income level. Together, these frameworks help researchers compare cancer burden across countries with differing levels of development, resources, health systems, and risk factor profiles, providing important insights into global cancer disparities and opportunities for prevention, early detection, and treatment.

Patterns of cancer incidence and mortality vary considerably across HDI categories. In 2024, female breast cancer was the most commonly diagnosed cancer across all HDI levels and in India, while lung cancer was the leading cancer diagnosis ranked first in China. Lung cancer was also the leading cause of cancer death across all HDI levels, China, and India, except in low-HDI countries, where female breast cancer was the leading cause of cancer death (61).

While colorectal and prostate cancers are common across most HDI levels, infection-related cancers account for a larger share of the cancer burden in lower-HDI countries. Cervical cancer, largely caused by HPV infection, is the second most commonly diagnosed cancer in low-HDI countries and third in medium-HDI countries. In India, lip and oral cavity cancer ranks second for incidence and third for mortality, highlighting the country's substantial oral cancer burden (61).

The *AACR Pediatric Cancer Progress Report 2025* highlights global trends in cancers affecting children and adolescents. Childhood cancer is a major worldwide health challenge, with the United States and other high-income countries (HICs) accounting for only 10 percent to 20 percent of cases. In contrast, approximately 80 percent to 90 percent of childhood cancers occur in low-income countries (LICs) and middle-income countries (65,66).

Escalating conflict in the Middle East may disrupt cancer medicine supply chains, as transportation routes and logistics networks are often adjusted to avoid conflict zones. These disruptions **can increase the cost of therapeutics** and other oncology-related supplies, **delay deliveries**, and **create challenges in maintaining a stable supply** of critical cancer care products.

Source: (64). W10

Clinical trials drive advances in childhood cancer outcomes. However, **fewer than 25% of all pediatric clinical trials are sponsored by countries in Africa or Asia**, where **survival rates** in many countries **are below 60%**.

Sources: (67,71). W11

Global childhood cancer patterns reveal substantial disparities in incidence and outcomes, largely influenced by differences in demographics, health care infrastructure, socioeconomic development, and timely access to diagnosis, treatment, and supportive care. For example, although treatment advances in HICs have dramatically improved survival, these gains have not been realized uniformly around the globe. While advances in HICs have achieved 5-year survival rates for childhood cancers of nearly 80 percent, survival rates in LICs and lower middle-income countries (LMICs) remain below 30 percent (67).

In 2025, the International Agency for Research on Cancer estimated more than 280,000 new pediatric cancer cases and nearly 108,000 deaths worldwide (68). However, these figures likely underestimate the true burden due to underdiagnosis and differences in data collection. Adjusted estimates suggest that the actual number of cases may be closer to 470,000, with approximately 113,000 deaths (66,69,70). Despite these limitations, available data provide critical insight into the global impact of childhood cancer.

Achieving equitable progress in cancer control requires stronger global collaboration to share best practices and develop locally relevant, innovative approaches. Aligning research investment with the global distribution of cancer burden and access to care is critical, alongside priorities in low-income and middle-income settings such as earlier diagnosis, improved access and outcomes, value-based care, implementation research, capacity building, and effective use of technology (72,73). Efforts should focus on preventing and treating infection-related cancers and expanding access to surgery and radiotherapy, which are critical for treating many solid tumors (74,75).

Funding Cancer Research: A Vital Investment

The immense toll of cancer is felt both in the number of lives it affects each year and its economic impact. The direct costs of cancer care, which include the cost of medical care and other services directly related to a cancer diagnosis, are just one measure of the financial impact of cancer. In the United

States, direct costs associated with cancer care in 2020 were estimated to be $236.2 billion (in 2022 dollars), corresponding to approximately $129,500 per cancer diagnosis (76). These costs are expected to rise as the US population grows and ages, with cancer-related medical costs in the United States projected to exceed $245 billion by 2030 (77).

Notably, direct medical costs do not include the additional burden of lost productivity due to cancer-related illness and premature death. Globally, premature cancer-related deaths among people ages 15 to 64 in 2022 were estimated to cost $566 billion in lost productivity, reflecting losses from paid work as well as unpaid activities such as caregiving, household responsibilities, and other contributions to families and communities (78). These productivity losses may be especially pronounced among those diagnosed at younger ages, for whom cancer can disrupt education, employment, and long-term earning potential (see **Childhood Cancer Survivors**, p. 149, and **Adolescent and Young Adult Cancer Survivors**, p. 152). For example, in the United States, lifetime productivity losses among adolescents and young adults diagnosed with cancer in 2019 were estimated at $18 billion, with the majority of these losses attributable to premature mortality and reduced workforce participation (79).

Individuals with cancer shoulder a large amount of the economic burden associated with cancer care (see **Financial Challenges**, p. 148). In 2019, the national patient economic burden associated with cancer care was estimated to be $21.1 billion, including $16.2 billion in out-of-pocket costs for cancer-related medical care and $4.9 billion in time costs, reflecting the value of time that patients spent traveling to and from health care, waiting for care, and receiving care (15,80).

With the number of new cancer cases projected to increase in the coming decades, both direct and indirect costs of cancer care are expected to rise substantially. One analysis estimated that cancer will cost the US economy $5.3 trillion over the next three decades (81). This rising economic toll underscores the urgent need for sustained investment in cancer research to accelerate progress across the cancer continuum and reduce the growing burden of cancer on patients, families, the health care system, and the broader economy.

As the burden of cancer continues to grow, federal research funding should be strategically aligned with areas of greatest clinical need. However, a recent analysis of nine major cancer types in the United States found that several highly lethal cancers, including cancers of the pancreas, liver, lung, and stomach, received disproportionately low funding from the National Institutes of Health (NIH) in fiscal year (FY) 2025 relative to their estimated mortality burden (82). Better alignment of federal research funding with areas of greatest unmet need could help accelerate progress against the most lethal cancers.

NIH-funded Research Fuels the US Economy

- In fiscal year 2025, **NIH awarded 58,795 grants totaling $36.58 billion to researchers** across all 50 states and Washington, DC.
- This funding **supported 390,863 jobs and generated $94.15 billion** in new economic activity.
- Every $1 invested in NIH research generated $2.57 in economic activity—a **250% return on investment**.

Source: (83).

W12

As the world's largest funder of medical research, NIH has long received bipartisan support from US lawmakers. For most of the past decade, consecutive budget increases have helped maintain the momentum of progress against cancer and other diseases. However, in FY 2024, NIH funding declined for the first time in nearly a decade and remained flat in FY 2025, marking 2 consecutive years without an increase in the agency's budget. At the same time, the cost of conducting medical research continues to rise because of inflation and other economic factors, as well as the increasing complexity of scientific investigations and clinical trials, which often require advanced technologies and highly specialized personnel. Although in FY 2026 NIH received a modest funding increase of approximately 1 percent over FY 2025 levels, this increase is unlikely to keep pace with rising research costs, potentially limiting the nation's capacity to support the full spectrum

The Impact of NIH Funding Disruptions

	FY 2024	FY 2025	CHANGE
Total NIH Research Funding	$36.94 billion	$36.58 billion	▼1.0%
Number of Grants Funded	64,359	58,795	▼8.6%
Number of Jobs Supported	407,782	390,863	▼4.1%

FY, fiscal year.
Source: (83).

W13

of research that drives advances in cancer prevention, early detection, treatment, and survivorship.

The medical research community also continues to face disruptions to previously awarded NIH funding. In early 2025, the Administration terminated support for more than 2,200 active NIH research grants and withdrew billions of dollars in previously awarded research funding (84). Training and career development programs were particularly affected, with hundreds of canceled awards intended to support graduate students, postdoctoral fellows, and early-career investigators (84,85). NIH grant terminations also disrupted hundreds of active clinical trials, including cancer-related trials, affecting more than 74,000 trial participants (86). The effects of these funding losses continue to reverberate across the medical research enterprise, threatening scientific progress, weakening the research pipeline, and delaying discoveries that could improve outcomes for patients with cancer and other diseases.

Compounding these challenges, in April 2026, the White House released the President's FY 2027 budget request, which proposed a $5 billion reduction in overall NIH funding compared to FY 2026 enacted levels (87). These proposed reductions come at a time when other nations are rapidly expanding their cancer research and drug development capacity, with some now outpacing the United States in high-quality cancer research output and oncology clinical trial initiation (88-90). Without strong federal support for medical research, the United States risks losing its position as a global leader in scientific discovery, innovation, and the development of lifesaving cancer treatments.

Discoveries fueled by NIH funding have transformed cancer prevention, detection, and treatment, turning a once-fatal diagnosis into a manageable chronic condition for many patients, saving millions of lives and offering hope to millions more. Sustained and predictable federal funding is essential to preserve US leadership in medical research, safeguard progress against cancer, support the development of the next generation of cancer researchers, and ensure that future generations continue to benefit from scientific breakthroughs in the quest to end cancer (see **AACR Call to Action**, p. 202).

Understanding the Path to Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- Cancer is a collection of diseases in which some of the body's cells acquire changes that allow them to grow uncontrollably and spread to other parts of the body.
- Basic research has played a pivotal role in understanding how cancer begins and spreads.
- Changes inside the cell and influences from outside the cell drive cancer initiation and progression.
- Technological advances have accelerated the identification of molecular and cellular mechanisms that drive cancer.
- Integrating the knowledge gained from decades of research into cancer development has fueled the field of precision medicine.

Precise molecular mechanisms control normal cell growth and division, which are required for development, regeneration, and overall healthy tissue and organ functions. In cancer, these mechanisms go awry, allowing cells to multiply uncontrollably and spread to other parts of the body. Cancer is not one disease, but a collection of related diseases that can affect nearly any part of the body. Throughout the course of cancer development, abnormal or damaged cells acquire distinct traits—known as the "hallmarks of cancer"—that set them apart from normal cells.

These hallmarks include the ability of cancer cells to divide limitlessly, disrupt normal regulation of cell growth, change identity and behavior, rewire metabolism to support rapid growth, resist cell death, stimulate blood vessel formation, evade the immune system, and leave the tissue of origin and spread to other organs (see **Figure 3**, p. 32) (91). Cancer that has spread to other parts of the body, which is called metastatic disease, is the main cause of most cancer-related deaths.

Generating Knowledge Through Basic Research

Basic research focuses on gaining new knowledge or a deeper understanding of phenomena or observable events. For example, basic research plays an essential role in characterizing normal cell behavior and identifying the changes that drive cancer initiation and progression. The knowledge gained from basic research deepens our understanding of cancer biology and provides a foundation for discovering new ways to target cancer cells, developing more effective treatments, and improving strategies for early detection and prevention. In recognition of the critical role of basic research in improving overall health for all individuals, more than 50 percent of the National Institutes of Health (NIH) budget was allocated to basic research each year from 2003 through 2024, the most recent year for which data are available (92).

Discoveries from basic research have transformed cancer care by revealing the fundamental biological mechanisms that drive cancer. For example, studies of cancer-causing viruses beginning in the early 1900s revealed genes that drive cancer development and laid the foundation for many modern targeted therapies (see **Basic Research Decoding Cancer's Complexities**, p. 34). These advances have depended on experimental models that allow researchers to study cancer under controlled conditions.

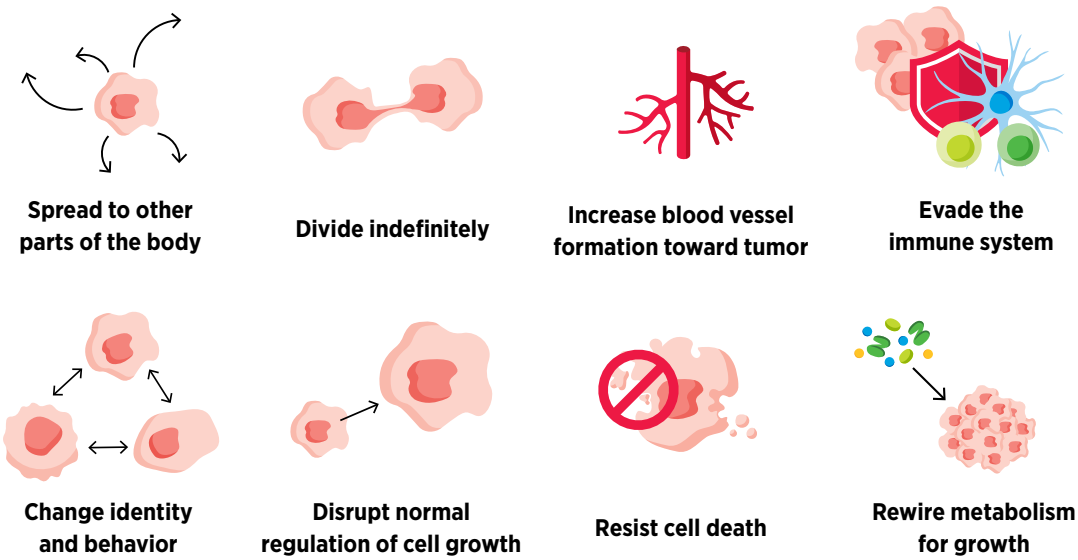
Researchers investigate cancer biology using a wide array of experimental models that mimic healthy and disease conditions (see **Sidebar 4**, p. 33). Studies using model organisms have uncovered fundamental biological processes that have shaped our understanding of cancer development. For decades, cancer research has relied heavily on animal models to study tumor development and evaluate potential

FIGURE 3

Hallmarks and Enabling Features of Cancer Cells

Hallmarks of Cancer Cells

Abilities cancer cells acquire to survive, grow, and spread



Enabling Features of Cancer Cells

Changes in cells and surrounding tissues that help cancer cells acquire these hallmarks

During the course of cancer development, abnormal or damaged cells acquire so-called "hallmarks" or characteristics that distinguish cancer cells from normal cells. These hallmarks include the ability to disrupt normal regulation of cell growth, divide indefinitely, rewire metabolism to support growth and survival, resist cell death, spread throughout the body, evade destruction by the immune system, stimulate blood vessel formation to support tumors, and change their identity and behavior to adapt to different environments and challenges.

Cancer development is further shaped by features that help tumors develop and evolve, including genetic instability, epigenetic changes, chronic inflammation, nerve signaling, and microbiome influences. In addition, cancer cells interact with surrounding cancer and supportive, non-cancer cells—including blood vessel, immune, and nerve cells, as well as cells that have become senescent—in the tumor microenvironment, which can influence how tumors grow, survive, and spread.

Source: (91).

SIDEBAR 4

Commonly Used Models in Cancer Research and New Approach Methodologies

To understand the biology of a disease, researchers use a variety of models that mimic what happens in healthy and disease conditions. Below are some of the most commonly used models in cancer research.

CELL LINES are cancer cells originally derived from tumors or tissues that have acquired, either naturally or through manipulation, the ability to grow indefinitely under laboratory conditions.

ORGANOIDS are engineered three-dimensional (3D) structures of cells generated from healthy or diseased cells that can be grown in a laboratory and resemble the structure, organization, and some of the functions of tissues and organs.

FRUIT FLIES (e.g., *Drosophila melanogaster*) are easily genetically modifiable organisms that share similarities to human signaling pathways and regulatory systems. They are widely used for studying mechanisms of tumor initiation and progression and for modeling specific cancer gene alterations.

ZEBRAFISH are small vertebrates that develop tumors that are histologically and genetically similar to human tumors and have transparent bodies that allow researchers to visualize tumor development in real time. They are widely used for studying tumor biology and testing drug responses.

MOUSE MODELS are used to study diseases (e.g., cancer development and responses to therapy). Genetically engineered models are created by introducing specific cancer-driving mutations into mice. Xenograft models are created by transplanting a patient's tumor or implanting cancer cell lines into mice.

New Approach Methodologies (NAMs)

NAMs encompass a diverse set of cell- and tissue-based (e.g., cell lines and organoids) and computational approaches, as well as certain non-mammalian animal models (e.g., zebrafish and fruit flies). Below are some of the emerging NAMs in cancer research.

CELL- AND TISSUE-BASED METHODOLOGIES:
Include cells, organoids, and engineered tissues maintained outside the body that allow researchers to investigate disease mechanisms, tissue organization, drug responses, and treatment toxicity.

- **Organ-on-a-chip models** are engineered devices containing living cells that can mimic the structure, function, and interactions of tissues and organs.
- **3D bioprinted models** are constructed by precisely arranging living cells and biomaterials to resemble tissues or organs.

COMPUTATIONAL METHODOLOGIES:
Include computer-based approaches that use mathematical modeling, simulations, and artificial intelligence (AI) to evaluate biological processes, predict outcomes, and support therapeutic development.

- **AI-based approaches** use data-driven learning to identify patterns and make predictions. They can also be used to create digital twins (virtual representations of patients) and to conduct *in silico* trials that simulate therapeutic responses in virtual environments.
- **Mathematical modeling approaches** use mathematical equations, simulations, and algorithms to represent biological systems and predict biological responses, disease progression, and therapeutic outcomes.

therapies. More recently, advances in tissue engineering, stem cell biology, biomaterials fabrication, and computational science have led to the emergence of new approach methodologies (NAMs), which can include non-mammalian animals, organoids, organ-on-a-chip systems, artificial intelligence (AI)–based applications, and other approaches that can complement and reduce reliance on traditional animal models.

Reflecting the growing potential of these approaches, NIH and the United States (US) Food and Drug Administration (FDA) have recently expanded efforts to broaden the use of NAMs in biomedical research (see **Rapidly Delivering Safe and Effective Therapies to Patients**, p. 187). Recent efforts include the launch of NIH's Office of Research Innovation, Validation, and Application, which coordinates NIH-wide efforts to advance NAMs, and the Complement Animal Research in Experimentation (Complement-ARIE) program, which supports the development, validation, standardization, and adoption of these approaches. In March 2026, NIH announced more than $150 million in funding to develop and scale NAMs, marking the first awards under the Complement-ARIE program (93). At the same time, FDA has announced plans to reduce reliance on animal testing for the development of certain drugs and issued guidance on incorporating NAMs into drug development and regulatory decision-making (94). Ongoing efforts are focused on defining the contexts in which NAMs can complement existing research models while addressing remaining barriers to their effective integration into biomedical research (91,95,96).

Findings and hypotheses stemming from basic research are fundamental to understanding what triggers cancer development, how cancer evades the body's defenses, and how cancer spreads within the body. Basic research plays a central role in the medical research cycle (see **Figure 4**, p. 35).

Collectively, knowledge gained from medical research has advanced cancer risk reduction, enabled innovations in early detection and diagnosis, and improved personalized treatments. These advances are contributing to progress against cancer that is saving lives and improving health outcomes for countless patients.

Basic Research Decoding Cancer's Complexities

Decades of basic research, and discoveries stemming from it, have provided the foundation for progress against cancer (see **Sidebar 5**, p. 36). More than 50 years ago, studies of cancer-driving viruses fundamentally changed our understanding of cancer. Researchers investigating how certain viruses caused tumors discovered that the cancer-driving genes carried by these viruses originated from normal genes already present in healthy cells. This landmark discovery established the concept that cancer can arise when changes in the body's own genes transform normal genes into cancer-driving oncogenes. Building on these discoveries, researchers identified the first human oncogenes, including three closely related RAS genes (*HRAS*, *KRAS*, and *NRAS*), revealing that mutations in these genes can drive cancer development.

One notable example of how these fundamental discoveries have transformed cancer care is the development of therapies targeting Kirsten rat sarcoma viral oncogene homolog (KRAS), a protein encoded by the *KRAS* gene (see **Figure 5**, p. 37). The *KRAS* gene is altered in roughly 30 percent of human cancers, including many pancreatic, lung, and colorectal cancers. Once thought to be an "undruggable" target because of its complex structure and function, KRAS has now become one of the most rapidly advancing areas of precision oncology, demonstrating how decades of basic research can lead to lifesaving therapies.

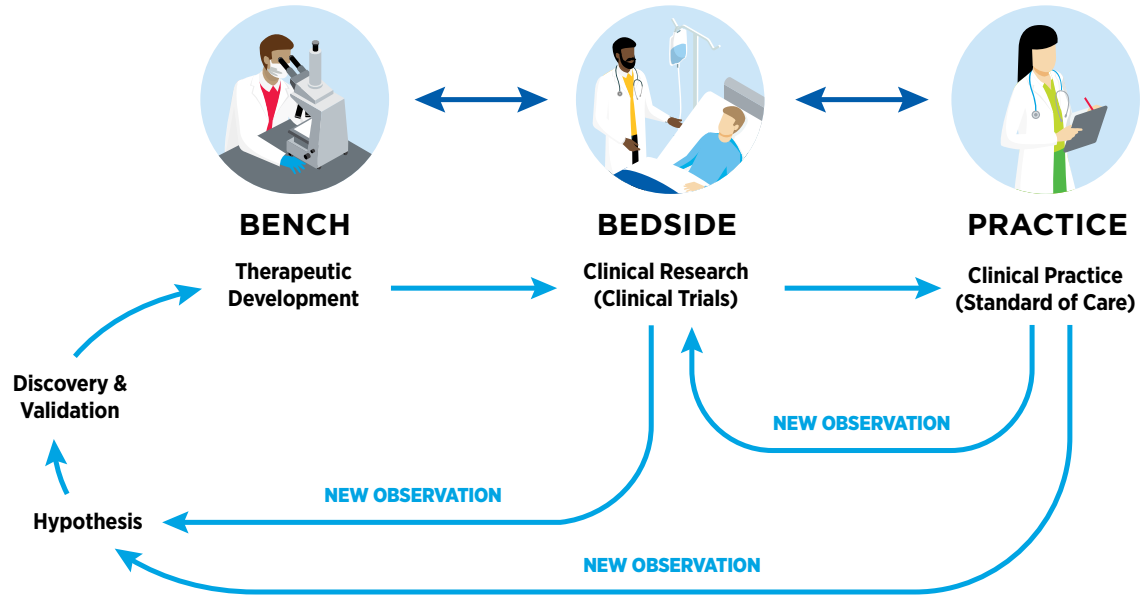
In 1982, researchers found that mutations in the gene could drive cancer development. Over the following decades, basic research revealed that the KRAS protein functions as a molecular switch that cycles between active and inactive states to regulate cell growth, survival, and other essential cellular processes. Mutations can cause the protein to be locked in the "on" position, allowing cells to grow uncontrollably. Although these discoveries established that *KRAS* mutations could drive cancer, the KRAS protein lacked binding pockets for therapeutic molecules to target, presenting a major challenge for drug development.

Progress toward overcoming this challenge was eventually made possible through a series of fundamental research breakthroughs. Advances in understanding the three-dimensional (3D) structure of proteins uncovered a hidden pocket on a mutant form of KRAS, called KRAS G12C, and new chemistry tools helped researchers design drugs that bind to that pocket and inhibit the protein's cancer-driving activity.

This breakthrough laid the foundation for the development of sotorasib (Lumakras), the first FDA-approved KRAS inhibitor for adults with *KRAS* G12C-mutated non–small cell lung cancer in 2021, nearly 40 years after the role of the *KRAS* gene in cancer was discovered. This milestone was quickly followed by the 2022 FDA approval of adagrasib (Krazati), a second KRAS inhibitor targeting the same mutation (see **Sidebar 48**, p. 174). As of June 30, 2026, sotorasib and adagrasib remain the only FDA-approved drugs targeting *KRAS*-mutated cancers, now approved for both lung and colorectal cancers, with ongoing research focused on enhancing their effectiveness and expanding their use across additional cancer types.

FIGURE 4

The Medical Research Cycle Driving Progress Against Cancer



The medical research cycle is a self-driven process whose primary goal is to save and improve lives. Findings from basic research lead to new questions; generate new hypotheses; and reveal new targets for developing better and more effective prevention strategies, early detection approaches, and treatments. Potential therapeutics can be designed against these new targets and tested for safety and efficacy in preclinical models that mimic normal and disease conditions.

If the potential therapeutic is safe and effective in preclinical models, it can then be tested in clinical trials and, based on the results of these studies, may be approved for use in the clinic by 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 the development of safer and more effective therapeutics, scientific knowledge gathered during the medical research cycle can also lead to evidence-based guidelines and strategies for cancer screening and prevention, as well as to changes in public health policies and regulations.

However, the impact of these foundational basic research discoveries extends far beyond these first-generation KRAS inhibitors. Next-generation KRAS inhibitors are advancing through clinical trials with improved potency, broader activity, and the ability to target additional *KRAS* mutations (e.g., the *KRAS* G12D mutation common in pancreatic cancer) or work more broadly against multiple forms of KRAS—known as pan-KRAS inhibitors (97). As one example, a recent phase III clinical trial showed that the pan-RAS inhibitor daraxonrasib significantly improved outcomes for patients with metastatic pancreatic cancer. Compared to standard chemotherapy, treatment with daraxonrasib doubled both median overall survival (13.2 vs. 6.7 months) and progression-free survival (7.3 vs. 3.5 months) (98).

Insights gained through decades of research are also driving the development of entirely new therapeutic approaches beyond KRAS inhibitors (99). These include protein degraders designed to eliminate KRAS proteins from cancer cells, vaccines that train the immune system to recognize *KRAS*-mutant tumors, engineered immune cells that selectively attack cancer cells carrying *KRAS* mutations, and combination strategies that simultaneously target multiple pathways involved in *KRAS*-driven cancers (100-104). Together, these approaches have transformed KRAS from a single therapeutic target into one of the most active areas of cancer drug development, with the potential to improve outcomes for patients with a wide range of cancers.

SIDEBAR 5

Basic Research Driving Clinical Advances Against Cancer

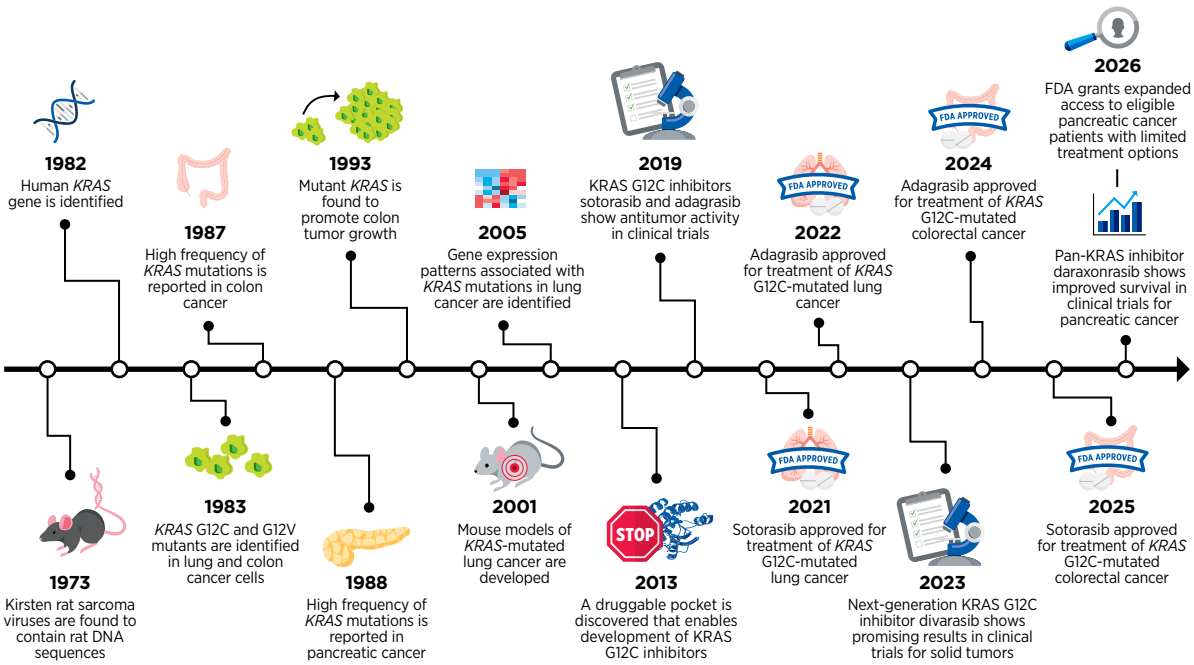
Basic Research Discoveries	Clinical Breakthroughs (As of June 30, 2026)
1980s The *HER2* gene is identified and sequenced.	Since FDA's 1998 approval of the first HER2-targeted therapy—trastuzumab (Herceptin)—to treat HER2-positive **metastatic breast cancer**, HER2-targeted therapeutics, alone or in combination with others, have been approved for treatment of certain types of **breast**, **stomach**, **lung**, **biliary tract**, and **colorectal cancers**, as well as **any solid tumor with a specific HER2 biomarker**.
1980s The *RET* gene is identified and its rearrangements in **thyroid cancer** are discovered.	Since FDA's 2020 approval of the first molecularly targeted therapeutic that inhibits RET activity—selpercatinib (Retevmo)—to treat **thyroid cancer**, two RET-targeted therapies have now been approved by FDA for treatment of **lung** and **thyroid cancers**, as well as **any solid tumor based on *RET* fusions**.
1980s The ubiquitin-proteasome system is discovered and its role in selectively degrading unwanted or damaged proteins is identified.	Several classes of drugs that target this pathway to eradicate cancer cells have been developed and approved by FDA, including the first proteolysis-targeting chimera (PROTAC) protein degrader therapy—vepdegestrant (Veppanu)—approved in 2026 to treat patients with a certain type of **breast cancer**.
1990s The *PDCD1* gene, which encodes the immune checkpoint protein PD-1, is identified.	Since FDA's 2014 approval of the first PD-1–targeted immune checkpoint inhibitor (ICI)—pembrolizumab (Keytruda)—to treat **melanoma**, it has been approved for the treatment of **17 additional cancer types**, as well as **any solid tumor with certain biomarkers**, and is the only ICI approved for the treatment of **cervical**, **ovarian**, and **breast cancers**.
2010s Histone H3 mutations, including H3K27M, are discovered to disrupt epigenetic regulation and identified as drivers of **diffuse midline glioma**, revealing new therapeutic vulnerabilities.	The first protease activator—dordaviprone (Modeyso)—was approved by FDA in 2025 to treat adult and pediatric patients with **diffuse midline glioma** harboring an H3K27M mutation. Notably, this is the first FDA-approved treatment specifically for H3K27M-mutant **diffuse midline glioma**.

Translating Knowledge to Understand the Biology of Cancer

Cancer development is a complex and multistep process shaped by interactions among influences outside the body, throughout the body, within tissues, and inside individual cells (see **Figure 6**, p. 38). Influences outside the body, including social drivers of health, behavioral risk factors (e.g., smoking and alcohol consumption), and environmental exposures (e.g., air pollution and environmental carcinogens), affect biological processes throughout the body and can contribute to the molecular and cellular changes that drive cancer initiation and progression. Factors such as aging, obesity, and chronic inflammation can also alter the surrounding tissue

FIGURE 5

Milestones in the Journey to Target the Once Undruggable KRAS



The role of the *KRAS* (Kirsten rat sarcoma viral oncogene homolog) gene in cancer was first demonstrated in 1982, launching decades of research that led to the evaluation of KRAS-targeted therapeutics that work directly (by inhibiting its function) or indirectly (by blocking other proteins that carry out its function). The first clinical trials investigating the indirect targeting of KRAS began in the early 2000s, but many approaches ultimately failed because of limited efficacy and/or toxicity. Targeting KRAS directly with small molecular inhibitors proved especially challenging because the protein lacked a "druggable" binding pocket. Deeper insights into three-dimensional protein structures and advances in drug design ultimately led to the development and approval of the first KRAS inhibitor by FDA, sotorasib (Lumakras), in May 2021 for adults with *KRAS* G12C-mutated lung cancer. In December 2022, FDA approved a second KRAS inhibitor, adagrasib (Krazati), for the same mutation. As of June 30, 2026, sotorasib and adagrasib remain the only FDA-approved drugs targeting *KRAS*-mutated cancers and are now both approved for the treatment of lung and colorectal cancers. Building on this success, next-generation KRAS-targeted therapies are advancing through preclinical studies and clinical trials. These include KRAS inhibitors with improved potency, broader activity, and the ability to target additional *KRAS* mutations or multiple forms of KRAS. At the same time, researchers are also developing KRAS protein degraders, vaccines, engineered immune cell therapies, and combination therapies approaches that could further broaden the therapeutic landscape for *KRAS*-driven cancers.

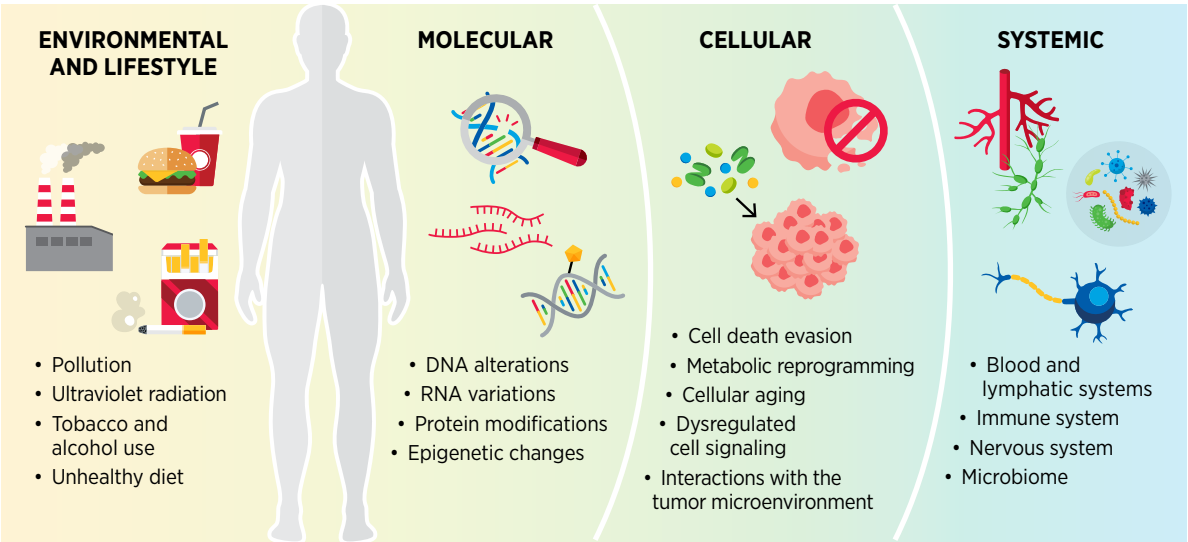
environment, further facilitating conditions that favor the growth and survival of cancer cells (105).

As cancer progresses, cells accumulate additional changes and evolve in ways that allow them to grow more aggressively and evade the immune system. Some of these changes allow cancer cells to switch between different cellular states in response to signals and changing conditions in their environment, a process known as cellular plasticity. As these changes accumulate, cancer cells become increasingly diverse.

This continuous evolution, along with cellular plasticity, leads to significant molecular and cellular differences among cells within a single tumor, a phenomenon known as tumor heterogeneity. As one example, researchers recently identified a rare population of highly adaptable cancer cells in lung tumors

FIGURE 6

Cancer Development: Influences Inside and Outside the Body



Cancer development is shaped by complex interactions across systemic, environmental, cellular, and molecular levels. Environmental and lifestyle exposures—including pollution, ultraviolet (UV) radiation, tobacco use, and diet—can influence biological processes such as aging, hormone signaling, metabolism, and chronic inflammation, all of which can contribute to cancer risk. Inside the body, systemic factors such as the blood, lymphatic, immune, and nervous systems, and the microbiome further shape cancer initiation and progression. At the cellular and molecular levels, DNA alterations, RNA variations, protein modifications, and epigenetic changes disrupt signaling pathways and metabolic processes leading to cancer development. Together, these interconnected processes influence if and how cancer arises.

that can generate diverse cell states and drive tumor growth, progression, and therapy resistance (106). Tumor heterogeneity also describes the differences that can exist between tumors arising in the same tissue type across different individuals, as well as among multiple tumors within an individual patient when the cancer has spread.

Understanding the cellular and molecular factors inside and outside the cell that influence cancer initiation and progression is key to developing more effective strategies for prevention and treatment.

Influences Inside the Cell

Cells store their genetic information in DNA, a double-helical molecule made of four chemical building blocks called bases: adenine (A), thymine (T), cytosine (C), and guanine (G). The complete set of a person's DNA is called the genome.

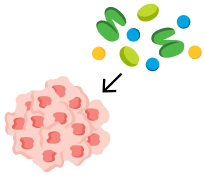
In human cells, DNA is wrapped around proteins called histones to form chromatin, which is further compacted into chromosomes. Most human cells contain 46 chromosomes. Each chromosome contains hundreds to thousands of genes, which are segments of DNA that carry the instructions for making proteins. Epigenetic modifications—chemical changes to DNA and histones—help regulate which genes are turned on or off, allowing cells with the same genome to develop into different cell types and perform specialized functions.

To make proteins, cells first copy the instructions encoded in DNA into a molecule called messenger RNA (mRNA) through a process known as transcription. The mRNA is then used as a template to produce proteins, which carry out most of the essential functions of cells. When the genetic instructions or the processes that read and interpret them are altered, the tightly regulated programs that control normal cell growth and function can break down, leading to cancer.

SIDEBAR 6

The Role of Cellular Metabolism in Cancer

Cellular metabolism refers to the chemical changes that take place inside cells to generate energy and build the molecules needed for growth, repair, and survival. These processes can be regulated by DNA, RNA, and protein-level mechanisms that determine how cells acquire, process, and use nutrients. Cellular metabolism can also be influenced by the availability of nutrients from the host's diet.



Metabolic rewiring by cancer cells contributes to cancer development by:

SUPPORTING RAPID GROWTH

Cancer cells require a steady supply of proteins, lipids, and other cellular building blocks. Metabolic adaptations allow cancer cells to redirect nutrients to sustain rapid growth.

PROMOTING SURVIVAL UNDER STRESS

Cancer cells frequently encounter low oxygen levels, nutrient shortages, and other stresses. Metabolic adaptations allow cancer cells to adjust how they acquire and use nutrients, helping them survive under challenging conditions.

SHAPING THE TUMOR MICROENVIRONMENT

Cancer cells can alter the levels of metabolites and other molecules in their surroundings. Metabolic adaptations allow cancer cells to modify their local environment and influence immune cells, blood vessels, and other nearby cells to promote tumor growth.

CONTRIBUTING TO TREATMENT RESISTANCE

Cancer cells often adapt their metabolism in response to therapies that disrupt their growth and survival. Metabolic adaptations allow cancer cells to withstand treatment-related stress and, in some cases, develop resistance to therapy.

Cellular metabolism is increasingly recognized as an important regulator of cancer initiation and progression. Because cancer cells often rely on altered metabolic pathways, researchers are exploring ways to target these metabolic vulnerabilities.

Sources: (107-109).

While genetic alterations are often permanent changes to the DNA sequence, many changes involving RNA, proteins, and epigenetic regulation, are more dynamic and can rapidly shift in response to internal and external influences. These molecular changes can also alter metabolic pathways, which determine how cells generate energy, use nutrients, and respond to stress. This metabolic rewiring is increasingly recognized as an important driver of cancer development (see **Sidebar 6**, p. 39). The following sections explore the types of changes within the cell that can lead to cancer development.

APPROXIMATELY 5%
OF ADULTS CARRY INHERITED
GENETIC VARIANTS
ASSOCIATED WITH CANCER RISK

Source: (110).

W14

Genetic Alterations

Genetic alterations, also called mutations or variants, include changes in the DNA sequence and can change the sequence or amount of the resulting mRNA and protein, thus disrupting or modifying normal protein function and contributing to cancer development. Genetic alterations can be inherited from parents (referred to as germline mutations) or acquired throughout a person's lifetime (referred to as somatic mutations) (see **Sidebar 7**, p. 40). Whether inherited or acquired, genetic mutations can disrupt normal cellular functions.

Germline mutations play a critical role in determining the inherited risk of developing cancer. About 10 percent of cancer

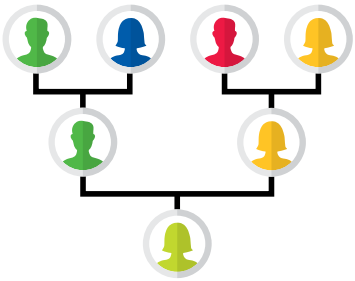
SIDEBAR 7

Genetic Alterations

Genetic alterations include changes in the DNA sequence. While not all genetic alterations cause cancer, some result in changes in the sequence or amount of messenger RNA and/or proteins produced that can drive or contribute to cancer development.

How Genetic Alterations Arise

GERMLINE MUTATIONS are inherited from parents.



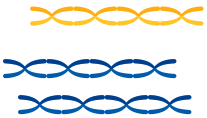
SOMATIC MUTATIONS are acquired during a person's lifetime and can arise from:

- Certain viral infections
- Smoking
- Extended exposure to ultraviolet (UV) radiation
- Environmental exposure to cancer-causing chemicals
- Errors made during normal cell division
- Naturally occurring DNA damage that accumulates over time
- Chronic inflammation fueled by medical conditions such as Barrett's esophagus or Crohn's disease

Types of Genetic Alterations That Contribute to Cancer Development

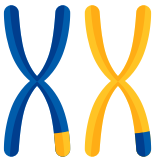
GENE GAIN OR AMPLIFICATION

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



STRUCTURAL VARIATION

Occurs when two separate genes or pieces of chromosomes join (called translocations or rearrangements) to produce a new protein or different amount of protein.



SINGLE BASE CHANGE

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

LARGE DELETION

Indicates loss of sections of genes or chromosomes, which can eliminate key regulators of normal cell growth and survival.

cases are caused by germline mutations. These mutations occur in the body's reproductive cells (egg or sperm) that are passed on from parents to children and can increase their risk of developing cancer; however, not all germline mutations contribute to cancer development.

Emerging technologies are expanding our ability to detect a wide spectrum of genetic alterations (see **Sidebar 8**, p. 41). Advances in DNA sequencing have enabled a better understanding of germline mutations that are associated with a person's risk of developing cancer. A recent study analyzing sequences of the protein-coding regions of the genome from more than 820,000 individuals identified inherited variants associated with breast cancer susceptibility, expanding the number of confirmed breast cancer predisposition genes (111). These findings may improve our understanding of hereditary breast cancer risk and offer new opportunities to inform risk prediction, prevention, and early detection strategies.

Inherited genetic variants can also influence how acquired mutations evolve over time. Clonal hematopoiesis is a condition in which blood stem cells acquire genetic mutations and give rise to genetically distinct populations of blood cells, and it can increase the risk of developing blood cancers. Research has identified inherited variants that increase susceptibility to clonal hematopoiesis, shape which mutated

SIDEBAR 8

Technologies Accelerating Discovery in Cancer Development

Innovative technologies are driving progress in cancer research by enabling the generation and analysis of diverse types of biological data, each offering unique insights into the molecular and cellular underpinnings of cancers.

Types of Technology*

TECHNOLOGY	IMPACT ON CANCER RESEARCH
Whole-genome sequencing (WGS): Provides the sequence of the entire genome.	Reveals both common and rare mutations across the genome, providing a comprehensive view of alterations that contribute to cancer development, including previously unknown alterations.
Whole-exome sequencing (WES): Provides the sequence of the entire "exome," the protein-coding regions of the genome.	Identifies variation in genes that may affect protein function and contribute to cancer development, providing a focused and cost-effective view of clinically relevant alterations in coding regions of the genome.
DNA methylation profiling: Detects chemical modifications to DNA.	Enables tumor classification, identifies methylation patterns driving cancer, and provides biomarkers for prognosis, capturing signatures that genetic data alone cannot.
RNA sequencing: Reads RNA molecules and measures gene expression.	Quantifies gene expression levels, detects fusion genes and tandem duplications, and identifies transcript variants, providing insight into dysregulated pathways driving cancer and can be used to refine diagnosis.
Single-cell analysis: Examines genomic, epigenomic, transcriptomic, or proteomic information in individual cells.	Captures differences between tumor and healthy cells or between individual cells within a tumor, revealing tumor heterogeneity and detecting cell-specific signals that could be missed in bulk cell analysis.
Spatial omics (e.g., spatial transcriptomics, spatial proteomics): Maps molecular information, such as gene and protein expression, across regions of intact tissues.	Provides context to how cancer cells are positioned in a tissue and how they interact within a spatial context, revealing heterogeneity and region-specific interactions and microenvironments.
Computational analysis and modeling tools: Use algorithms to integrate omic datasets and model the biology of cancers.	Predict cancer biology, therapy-driven tumor evolution and treatment responses, and progression to metastatic disease, as well as integrate complex datasets into testable hypotheses.

Types of Biological Data*

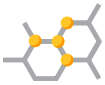
EPIGENOMIC data detail epigenetic changes in cells, including DNA methylation and histone modifications, which can reveal how gene regulation is altered in cancer.

GENOMIC data detail the sequence of DNA in a biological sample, which can reveal genetic alterations that drive cancer development.

METABOLOMIC data detail the small molecules that cells produce and use for energy, which can reveal how cancer cells change their metabolism to grow, survive, and resist treatment.

PROTEOMIC data detail all proteins in a biological sample, including their quantities and structures, which can reveal disease markers and therapeutic targets in cancer.

TRANSCRIPTOMIC data detail all RNA molecules in a biological sample, which can reveal which genes are turned on or off in cancer cells.



MULTI-OMIC data integrate multiple "omic" measures that can provide a comprehensive view of the molecular changes underpinning cancer biology. For example, proteogenomics combines genomic, transcriptomic, and proteomic data to link DNA and RNA alterations to protein expression.

* This list presents a selected set of technologies and biological data that are accelerating discovery in cancer research and is not intended to be comprehensive.

cells expand, and influence the likelihood that these cells progress to blood cancers (112,113).

However, inherited genetic variation does not always increase risk. A recent study identified an inherited variant that reduced the likelihood of clonal hematopoiesis. Researchers found that this variant limited the expansion of mutated blood cells, reducing the risk of clonal hematopoiesis and certain blood cancers. These findings highlight how inherited genetic variation can influence cancer risk not only by increasing susceptibility but also by promoting resilience to cancer-associated cellular changes (114).

Large-scale genome-wide association studies—which can analyze millions of genetic variations associated with disease risk—are identifying cancer risk variants at an unprecedented scale. As one example, in the largest genome-wide association study of high-grade serous ovarian cancer to date, researchers analyzed over 22 million genetic variants from nearly 400,000 women and identified seven previously unknown genomic regions associated with disease risk, improving models used to predict inherited susceptibility (115).

Somatic, or acquired, mutations arise during an individual's lifetime as a result of naturally occurring DNA damage, errors during normal cell division, or in response to environmental exposures, lifestyle factors, or chronic health conditions. These mutations contribute to the unique genetic landscape of individual tumors, with distinct patterns reflecting potential causes of cancer, tissue of origin, and evolution over time.

Somatic mutations accumulate throughout normal tissues over the course of life. Recent advances in highly sensitive DNA sequencing technologies have allowed researchers to identify cancer-associated driver mutations and clonal expansions in normal oral and bladder tissue that would not have been detectable using conventional sequencing approaches (116,117). While clonal hematopoiesis is a well-recognized example of how aging can reshape blood cell populations, similar processes are increasingly being identified in solid tissues. For example, researchers recently found that otherwise normal pancreatic tissue may harbor hundreds of pancreatic intraepithelial neoplasias (PanINs)—the most common precursors to pancreatic cancer. They found that nearly all PanINs contained cancer-associated somatic mutations and the adult pancreas can harbor hundreds of these lesions. Because pancreatic cancer remains relatively uncommon despite this high burden of precursor lesions, they suggest only a small fraction of PanINs progress to invasive cancer (118). Together, these findings suggest that genetically altered cells and precursor lesions may be far more common than previously thought, with important implications for cancer risk assessment, early detection, and prevention efforts.

Recent research has emphasized the importance of understanding how somatic mutation patterns can vary by age, as these differences may influence cancer initiation, progression, and response to treatment. The incidence of early-onset cancers, defined as cancers diagnosed in individuals ages 18 to 49, is growing globally (see **The Growing Population Burden of Cancer**, p. 23). A large international study of more than 17,000 colorectal cancer (CRC) patients found that tumors in younger adults often carry different genetic alterations than those diagnosed later in life. These findings support the need for age-informed molecular profiling that may inform future approaches to cancer diagnosis and treatment (119).

A recent study found that **systemic cancer therapy can contribute to mutations even in healthy tissue, including some that can drive cancer**, highlighting how treatment can shape the evolution of healthy cells.

Source: (120).

W15

In addition to germline and somatic DNA sequence mutations, structural genomic alterations—including chromosomal rearrangements and nontraditional DNA structures—can also influence cancer development. For example, chromosomal rearrangements can generate cancer-causing gene fusions, in which parts of two genes become joined to create a hybrid gene that produces an abnormal fusion protein capable of driving cancer development.

Extrachromosomal DNA (ecDNA)—circular DNA fragments that exist outside chromosomes—is an example of a nontraditional DNA structure that has emerged as a key contributor to tumor growth, treatment resistance, and poor clinical outcomes across cancer types. By carrying genes that regulate cell growth and survival, ecDNA acts as a potent driver of cancer progression. Unlike chromosomal DNA, ecDNA does not follow the normal rules of inheritance during cell division, enabling rapid amplification of cancer-promoting genes and allowing cancer cells to adapt more easily to treatments and other stresses in the tumor microenvironment.

Cutting-edge technologies and computational analysis tools have revealed that ecDNA is present in approximately 17 percent of human cancers, although the prevalence varies considerably across cancer types. For example, ecDNAs have been detected in 30 percent of pediatric neuroblastomas and 49 percent of adult glioblastomas, but in only 3 percent of kidney cancers (121). Just in the past year, notable progress has been made in ecDNA detection (122) and our understanding of how ecDNA contributes to cancer development, including its role in driving oncogene overexpression (123,124), increasing tumor

heterogeneity (125,126), promoting immune evasion (127), and enabling resistance to therapy (124).

New research has revealed several potential therapeutic vulnerabilities in ecDNA-driven cancers. These include dependencies on pathways that help cells resolve conflicts between the cell's DNA copying and RNA producing machineries, mechanisms that maintain ecDNA structure and inheritance during cell division, and molecular interactions that enable ecDNA to drive high levels of oncogene expression (128-131). Reflecting the importance of ecDNA, the Cancer Grand Challenges, a global multidisciplinary research initiative, is funding research into how ecDNA forms, functions, and can be targeted in cancer (see **Technological Innovations and Collaborative Science**, p. 50).

Researchers are building on the understanding of genetic alterations that drive cancer development to inform new strategies for cancer prevention, diagnosis, and treatment. Over the past two decades, FDA has approved numerous targeted therapies designed to inhibit the effects of specific genetic alterations found in cancer cells (132).

At the same time, genetic tests that detect germline mutations are helping individuals understand their inherited cancer risk, guiding clinical decisions, and supporting proactive health management for both patients and their families (see **Advances in Genomics-based and Risk-stratified Precision Approaches**, p. 93).

RNA Variations

Gene expression is the process by which a cell reads the instructions in a gene to produce mRNA. Cells can regulate this process to increase or decrease mRNA production as needed to respond to internal and external signals. In cancer, these regulatory processes often go awry.

Most genes are made up of alternating DNA segments known as exons and introns. Exons contain the instructions needed to make proteins, whereas introns do not. When a gene is transcribed into mRNA, the resulting transcript includes both exons and introns. Through a "cut and paste" process called RNA splicing, introns are removed and exons are joined together to produce an mRNA molecule that can then be translated into a functional protein. Cells also use a mechanism called alternative splicing to produce mRNAs with different combinations of exons from a single gene, generating multiple protein variants with distinct cellular functions.

If errors occur during RNA splicing, faulty mRNAs can produce dysfunctional proteins. In a recent study, aberrant splicing driven by loss of the *MEN1* gene was found to play a critical role in driving cancer growth and metastasis in lung cancer (133). Researchers are exploring the potential of targeting RNA splicing mechanisms as innovative therapeutic strategies to restore normal splicing patterns or selectively eliminate aberrant splice variants that are associated with cancer (134,135).

In addition to mRNA, cells also produce non-coding RNAs (ncRNAs)—RNA molecules that do not encode proteins but play critical roles in regulating gene expression. These include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), each of which can drive normal cellular processes but also influence how tumors grow, interact with their environment, and resist treatment (136-138).

While some RNA variations arise from changes in how RNA molecules are processed or regulated, such as aberrant splicing or dysregulated ncRNAs, others reflect the downstream effects of genetic alterations in DNA. Understanding how tumors change at the RNA level therefore provides vital insights into how cancer develops, evolves, and spreads. Advances in transcriptomic and RNA sequencing technologies are being used to identify and understand RNA-level changes by mapping how genes are expressed within individual tumor cells and across different regions of a tumor (see **Sidebar 8**, p. 41).

A growing proportion of lung cancer cases are being diagnosed in individuals who have never smoked (see **The Growing Population Burden of Cancer**, p. 23) (53). Although previous studies have identified many genetic alterations associated with these cancers (139), less is known about how these tumors differ at the transcriptomic level. In a recent study, researchers conducted a large-scale transcriptomic analysis of tumors from more than 680 never-smoker lung cancer patients and identified three distinct transcriptomic subtypes with unique gene expression patterns and cellular characteristics associated with differences in clinical outcomes (140). These findings may help guide the development of more personalized approaches to diagnosis and treatment in this patient population.

Additionally, researchers are using RNA sequencing to reveal the functional consequences of genetic alterations at the RNA level, helping to advance precision medicine. In a study of more than 2,300 children and adults with a wide range of solid tumors and blood cancers, targeted RNA sequencing identified clinically relevant RNA alterations that refined diagnoses and informed treatment decisions in 87 percent of cases (141).

As researchers continue to uncover how RNA variations contribute to cancer development, these discoveries are opening new therapeutic opportunities. Advances in RNA biology are enabling the development of RNA-based medicines that can regulate gene expression, produce therapeutic proteins, and stimulate antitumor immune responses (see **RNA Medicines**, p. 175).

Protein Modifications

Proteins are vital for normal cellular functions. The human genome contains approximately 20,000 protein-coding genes, and the full set of proteins expressed by the cell is known as the proteome. Proteomics is the study of the proteome, which can provide new insights into cancer biology and reveal molecular features that may help guide diagnosis and treatment.

Researchers recently expanded on earlier proteomic studies, which mostly focused on individual cancer types, by generating a pan-cancer proteomic atlas comprising more than 9,600 proteins from nearly 1,000 tumors representing 22 cancer types. This comprehensive resource revealed both shared and cancer-specific molecular features and identified potential biomarkers and therapeutic targets (142).

Proteogenomic research integrates protein data with genomic, transcriptomic, and other molecular data to provide a more comprehensive view of the molecular changes driving cancer than any single type of analysis alone (see **Sidebar 8**, p. 41). Researchers recently analyzed nearly 400 tumors from patients with medulloblastoma—a fast-growing brain cancer common in children and young adults—revealing previously unrecognized tumor subtypes based on their protein and metabolic features, uncovering biological insights not apparent from genomic and transcriptomic analyses alone, and identifying a therapeutically targetable metabolic vulnerability (143).

The functions of many proteins are regulated by posttranslational modifications (PTMs), which are reversible chemical changes that modulate protein function, localization, and stability. Advances in AI are accelerating research across the cancer continuum (see **Artificial Intelligence**, p. 166), including in cancer proteomic research. Researchers have recently developed an AI model, trained on a dataset containing nearly 400,000 experimentally validated PTM sites, to predict how genetic variants alter PTMs (144). This approach provides new insights into how genetic alterations can disrupt protein regulation and influence disease-associated biological processes, including those involved in cancer development.

Proteins carry out nearly all the cell's functions and must be located in the right place, in the correct 3D structure, and precisely controlled to function correctly. When proteins are no longer needed or become damaged, cells rely on carefully controlled degradation systems to remove them. Recent research has shown that disruption in the normal protein degradation pathway can contribute to therapeutic resistance. For example, researchers found that impaired degradation of KRAS protein promoted resistance to KRAS-targeted therapies in lung cancer (145). They also identified combination treatment strategies that restore drug sensitivity by blocking signaling pathways activated by impaired KRAS degradation, highlighting potential approaches for overcoming therapeutic resistance.

Researchers are also harnessing the cell's natural protein degradation machinery as a therapeutic strategy. For example, proteolysis-targeting chimeras (PROTACs) are a new class of therapeutics designed to selectively tag disease-causing proteins for destruction by the cell's protein degradation system. In May 2026, the first PROTAC therapy, vepdegestrant (Veppanu), was approved by FDA for patients with a certain type of breast cancer (see **Advances in Treatment With Molecularly Targeted Therapeutics**, p. 117). This milestone demonstrates how a deeper understanding of protein degradation pathways can lead to new treatment approaches for cancer.

Epigenetic Changes

Epigenetic modifications are chemical changes that regulate how genes are expressed without altering the underlying DNA sequence. The entirety of epigenetic changes within a cell is called the epigenome. Epigenetic changes are shaped by aging, environmental exposures, behavioral and lifestyle factors, and chronic stress. In healthy cells, these mechanisms help to tightly regulate gene expression, but in cancer this regulation is disrupted.

One common type of epigenetic alteration is DNA methylation, in which methyl groups are added to specific regions of the genome to regulate whether nearby genes are turned on or off. Other epigenetic changes, such as chemical modifications of histone proteins and changes in chromatin organization, also influence how genes are expressed and can contribute to cancer development.

In 2021, the World Health Organization published an updated classification of central nervous system (CNS) tumors that recognized DNA methylation profiling as an important tool for classifying and diagnosing these tumors, providing more precise tumor classification than traditional tissue morphology-based analysis and reducing unclear diagnoses (146). Building on this, researchers recently expanded a widely used DNA methylation–based classification system for CNS tumors by incorporating newly identified tumor subclasses defined by distinct DNA methylation patterns, more than doubling the number of recognized subclasses and improving the identification of rare and previously unrecognized tumor types that can inform clinical decision-making (147).

Methylation profiles are also increasingly being coupled with AI to improve diagnostic speed and accuracy. Recently, an AI-assisted framework was developed that uses DNA methylation patterns to classify acute leukemias, a group of aggressive blood cancers that require prompt diagnosis and treatment. The approach identified dozens of distinct

leukemia subtypes and accurately classified patients within hours, which could accelerate treatment planning and potentially limit treatment delays (148).

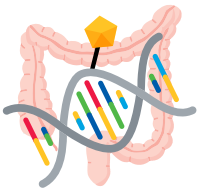
Research has also shown that DNA methylation profiles can help predict response and survival in certain patients treated with immune checkpoint inhibitors (ICIs) (see **Releasing the Brakes on the Immune System**, p. 132). In a recent study, researchers identified four tumor subtypes of pleural mesothelioma, an aggressive cancer often linked to asbestos exposure (see **Limit Exposure to Environmental Risk Factors**, p. 74), with increasing levels of methylation that differed in immune activity and clinical outcomes. They found that tumors with lower levels of DNA methylation showed a more active immune microenvironment and were associated with better responses to ICI therapy and longer survival, whereas highly methylated tumors exhibited features associated with immune suppression and poorer survival (149).

Epigenetic regulation is also influenced by aging, the immune system, and chronic stress. Researchers often refer to epigenetic clocks as an estimate of a person's biological age based on their DNA methylation patterns. When an individual's biological age outpaces their chronological age—known as epigenetic age acceleration—it may signal increased cancer risk. A recent study found that accelerated biological aging, measured by DNA methylation–based epigenetic clocks in blood cells, was associated with an increased risk of developing CRC in postmenopausal women (150). These findings suggest that epigenetic aging biomarkers could help identify individuals at elevated risk for developing cancer in an aging population.

Emerging evidence suggests that epigenetic aging may also play a role in the development of early-onset CRC. Research has found that patients with early-onset CRC exhibit epigenetic changes linked to chronic inflammation and accelerated epigenetic aging, having, on average, an epigenetic age 12 years older when compared to the average-onset CRC patients (152).

Research has significantly advanced our understanding of how the epigenome is modified in cancer and how these changes contribute to cancer development. A unique feature of epigenetic changes is that they are dynamic and reversible, making them attractive targets for cancer treatment. Consequently, several anticancer drugs that modify the cancer epigenome have been developed and approved by FDA.

Chronic inflammation can leave a lasting epigenetic "memory" in the colon, even after inflammation is resolved, **increasing the risk of colorectal cancer** if cancer-promoting mutations later occur.



Source: (151).

W16

Influences Outside the Cell

In addition to alterations inside the cell, influences outside the cell contribute to cancer initiation, progression, and response to therapy (see **Sidebar 9**, p. 46). These external factors include systemic influences, such as hormones and nutrients in circulation, as well as local tissue environments that interact continuously with tumor cells. 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 (91). This process—known as metastasis—is enabled by the blood and lymphatic systems, which provide physical routes through which cancer can spread, and the immune system, which can either suppress or support tumor progression, depending on how it is activated or suppressed.

Emerging evidence also shows the nervous system plays an active role in the ability of tumor cells to invade surrounding tissues and communicate with distant organs, influencing tumor growth, invasion, and metastasis. The microbiome—comprising a diverse community of microorganisms residing on and in the body—can influence cancer development by modulating inflammation, immune responses, and systemic metabolism. The tumor microenvironment (TME) encompasses the cellular and structural context in which a tumor exists and shapes how cancer evolves and responds to treatment. The following sections describe the influences outside the cell that can contribute to cancer development.

Blood and Lymphatic Systems

The blood and lymphatic systems are composed of interconnected networks of vessels, circulating cells, signaling molecules, and lymph nodes, as well as several organs, including the spleen, thymus, tonsils, and adenoids. Together, these networks deliver oxygen and nutrients throughout the body, remove cellular waste from tissues, and support the immune system. Additionally, blood and lymphatic vessels provide pathways through which cancer cells can spread from the primary tumor to other parts of the body.

One hallmark of cancer cells is the ability to promote angiogenesis—the formation of new blood vessels—toward and within a tumor, increasing tumor vascularization to help supply the oxygen and nutrients needed to support tumor growth. Unlike normal blood vessels, these newly formed tumor-associated blood vessels are structurally and

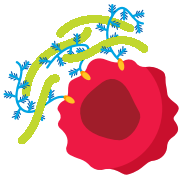
SIDEBAR 9

Cancer Growth: Local and Systemic Influences

Solid tumors are much more complex than an isolated mass of dividing cancer cells. Cancer development is strongly influenced by local and systemic interactions between cancer cells and numerous factors, including:

A NETWORK OF ABNORMAL BLOOD AND LYMPHATIC VESSELS in and around the tumor, stimulated by cancer cells through a process called tumor angiogenesis, helps support tumor growth and provides an escape route for cancer cells to spread to distant sites (metastasis).

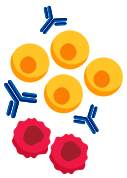
A MATRIX OF PROTEINS that surrounds tumor cells and provides structural and biochemical support. Formed partly in response to chemical signals from cancer cells, this matrix regulates the proliferation of cancer cells, supports tumor growth, and can help tumors evade attack by antitumor immune cells and aid in tumor metastasis.



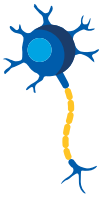
TUMOR MICROENVIRONMENT–ASSOCIATED CELLS that are not immune cells—such as pericytes, endothelial cells, cancer-associated fibroblasts, myofibroblasts, astrocytes, and platelets—can also support tumor growth by stimulating tumor cell multiplication, triggering formation of new blood vessels, and enhancing survival of cancer cells.

SYSTEMIC FACTORS in the bloodstream, such as growth factors (e.g., hormones), cytokines, and nutrients, influence the development and growth of cancer.

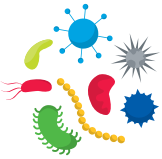
IMMUNE CELLS, some of which can identify and eliminate cancer cells, although in many cases cancer cells acquire characteristics that help them evade the immune system, permitting the formation and progression of a tumor.



NERVE FIBERS infiltrate tumors and can release neurotransmitters that influence cancer cell proliferation, migration, and immune evasion. Tumor–nerve interactions have been implicated in tumor growth, metastasis, and therapy resistance.



MICROORGANISMS can alter the immune response, influence inflammation, and affect cancer development and treatment response. These microbial communities interact with tumor and immune cells in ways that may promote or inhibit cancer progression.



functionally abnormal. Cancer cells can produce and release high levels of vascular endothelial growth factors (VEGF), a family of signaling proteins that stimulate angiogenesis. Over the past two decades, several drugs that block angiogenesis have been approved to treat cancer (153).

In addition to supporting tumor growth, these abnormal tumor-associated blood vessels can limit immune cell infiltration and contribute to an immunosuppressive TME, limiting the effectiveness of immunotherapies. Emerging evidence suggests that combining anti-angiogenic therapies with immunotherapy may help normalize tumor vascularization and improve treatment responses (154).

Advances in our understanding of the cellular and molecular mechanisms driving angiogenesis are informing the development of novel therapeutic strategies. For example, researchers have recently identified a novel pathway regulating blood vessel growth in endometrial tumors. They found that targeting a key regulator of this pathway reduced angiogenic signaling and slowed tumor growth in preclinical models (155).

Tumors can also increase the formation of new lymphatic vessels—a process known as lymphangiogenesis—that increase opportunities for cancer cells to access and spread through the lymphatic system, particularly to nearby lymph nodes. To initiate this process, tumor cells release signaling molecules that help them move toward nearby lymphatic vessels. As they enter the lymphatic network, cancer cells can accumulate in one or more regional lymph nodes. The detection of cancer cells in lymph nodes is a key factor in determining the stage and extent of disease. From the lymph nodes, cancer cells can enter the bloodstream or continue through the lymphatic system, enabling their spread to distant organs and tissues.

Two recent studies have shown that cancer cells actively remodel the lymph node microenvironment after metastasizing

to regional lymph nodes. Researchers found that in breast and head and neck cancers, metastatic tumor cells can alter the composition and function of lymphatic vessels within lymph nodes while reshaping local immune environments in ways that impair antitumor immune responses (156,157). These changes may help create conditions that support further cancer growth and metastasis.

Emerging research suggests that systemic factors such as **chronic psychological stress can influence cancer development** by suppressing antitumor immune responses and weakening immune surveillance.

Source: (161).

W17

Immune System

The immune system plays a critical role in fighting infections and other diseases, including cancer. Multiple cell types, tissues, and organs make up the immune system and work together to defend the body against pathogens (e.g., viruses and bacteria) and diseases (e.g., cancer), as well as remove abnormal or damaged cells from the body.

The immune system has two main components. The innate immune system includes physical barriers, such as the skin and mucous membranes, as well as certain immune cells and molecules that respond to and kill a broad range of pathogens. In contrast, the adaptive immune system provides a specific response against pathogens and remembers them for a faster response in case of a future encounter. Some key immune cells include dendritic cells that detect threats and alert the immune system to respond, T cells that can kill infected or abnormal cells and help coordinate the immune response, and B cells that produce antibodies to neutralize pathogens (see **Sidebar 36**, p. 132).

Although many abnormal cells are eliminated by the immune system, as cancer progresses, some cancer cells acquire properties that allow them to evade immune detection and destruction. Researchers have identified several mechanisms by which these cells evade the immune system, including activating immune checkpoints that suppress T-cell responses, recruiting immunosuppressive cells, and releasing proteins and signaling molecules that impair immune cell function (158).

In other cases, cancer cells can alter signaling pathways and metabolic interactions within the TME to suppress immune responses. A recent study found that tumor-associated macrophages, a type of immune cell, can provide metabolic support that helps glioblastoma cells suppress immune responses (159). In another study, researchers showed that cancer cells can hijack mitochondria—the energy-producing structures inside cells—from immune cells, impairing immune response and helping tumors spread to nearby lymph nodes (160).

Researchers continue to explore therapeutics that target immune escape mechanisms. ICIs, for example, block proteins that tumors use to suppress T-cell activity, unleashing the immune response (see **Sidebar 37**, p. 133). In a recent study, researchers identified a previously unrecognized immune checkpoint that limits T-cell activity within tumors. They found that selective serotonin reuptake inhibitors (SSRIs), a class of antidepressant drugs, enhanced T-cell antitumor activity and improved responses to ICI therapy in preclinical models by blocking this pathway, highlighting the potential to repurpose existing drugs to improve cancer immunotherapy (162). As our understanding of the complex interactions between cancer and the immune system continues to grow, so does the potential to develop more effective and lasting therapies.

Nervous System

The nervous system—composed of the CNS, which includes the brain and spinal cord, and the peripheral nervous system (PNS), a network of nerves that connects the CNS to the rest of the body—uses electrical signals and chemicals to regulate and coordinate essential functions. Recently, the nervous system has become more recognized as a key regulator of cancer development not only in brain tumors but also across cancer types, including pancreatic, breast, stomach, colorectal, lung, and prostate cancers (163).

Research has uncovered dynamic interactions between the nervous system, the immune system, and cancer as drivers of tumor growth, metastasis, immune evasion, and resistance to therapy, giving rise to the emerging interdisciplinary field of cancer neuroscience. These interactions take place both within the local TME and systemically throughout the body.

Nerve cells, or neurons, interact with cancer and non-cancer cells by releasing signaling molecules and transmitting electrical signals through direct contact within the TME. Recent studies have shown that tumors can actively remodel nearby nerves and promote cancer development. For example, using single-cell and transcriptomic technologies (see **Sidebar 8**, p. 41), researchers mapped the cellular interactions surrounding nerves in pancreatic tumors and found that cancer cells reprogram nearby nerve-associated cells and reshape local stromal and immune environments, creating a local environment that supports tumor progression (164).

Research has found that lung cancer cells communicate with the nervous system in multiple ways. Two recent studies

showed that small cell lung cancer cells can interact with nearby peripheral nerves through neurotransmitter signaling, including by forming functional neuron–tumor connections that promote tumor growth (165,166). In another study, researchers showed that lung tumors can also communicate with the brain through sensory nerves, triggering signals from the brain back to the tumor that suppress immune responses and promote tumor growth (167). In all three studies, disrupting these neural interactions reduced tumor growth in preclinical models, highlighting cancer–nerve communication as a potential therapeutic target.

Researchers have also uncovered important roles for the nervous system in regulating antitumor immunity. In stomach cancer, researchers found that neural signaling reprogrammed tumor metabolism, altered communication with immune cells, and promoted an immunosuppressive environment (168). In another study, researchers showed that cancer-induced nerve damage can trigger an inflammatory repair response that was associated with resistance to immunotherapy across multiple cancer types (169).

Scientists are discovering new ways in which the nervous system influences cancer progression. Factors such as nerve activity, brain chemical signaling, and disruption to the body's internal clock are being explored for their roles in promoting cancer cell proliferation, survival, and immune evasion.

Microbiome

The microbiome is made up of all the microbes—bacteria, fungi, viruses, and other microorganisms—that live on and in the skin, mouth, gut, and other sites in the body. Studies have shown that microbiomes play essential roles in digestion, metabolism, immune system regulation, and protection against pathogens. A growing body of research suggests that these microbial communities also influence cancer development and treatment response by shaping immune activity, inflammation, and the TME (91). While many early studies focused on the gut microbiome, scientists are now recognizing the importance of microbiomes in other tissues and organs, each with its own distinct microbial communities (170).

Research has shown that changes in the composition of the gut microbiome can contribute to the initiation and progression of colorectal, stomach, liver, pancreatic, breast, and prostate cancers (171). Beyond the gut microbiome's role in cancer development, certain gut microbes and microbial metabolites can also affect response to cancer treatment (see **Sidebar 10**, p. 49).

Recent studies have shown that modulating the gut microbiome may improve the effectiveness of cancer immunotherapies (see **Releasing the Brakes on the Immune System**, p. 132). One approach is fecal microbiota transplantation (FMT), a procedure in which stool from a donor is transferred to a patient to introduce beneficial microbes to the gut. Three landmark clinical trials recently demonstrated the promise of this approach. In patients with melanoma, kidney, and lung cancers, FMT was combined with immune checkpoint inhibitor therapy and showed encouraging signs of improving responses to treatment (184-186). Other research suggests that microbiome modulation may also improve chimeric antigen receptor (CAR) T-cell therapies. For example, a recent study found that supplementing with specific bacterial species enhanced the effectiveness of CAR T-cell therapy in preclinical models (187).

Beyond the gut, researchers have found that the oral microbiome may contribute to cancer development in distant organs. Certain oral bacteria have been identified within breast tumors that promote cancer tumor growth and metastasis by inducing inflammation and DNA damage (188). However, more research is needed to further characterize the microbiome inside tumors and determine their influence on cancer development.

It is becoming increasingly clear that targeting the microbiome may help improve health outcomes for patients with cancer (189). Efforts are now underway to manipulate the microbiome through strategies such as specifically designed mixtures of beneficial bacteria (probiotics), dietary supplements that nourish helpful microbes (precision prebiotics), and engineered bacterial species that deliver therapies or modulate immune signaling.

Tumor Microenvironment

The TME—composed of cancer and supportive, non-cancer cells, blood vessels, signaling molecules, and structural components—is a dynamic biological system that influences tumor growth, metastasis, and response to treatment. Cancer cells shape this environment by releasing molecules that secure nutrients, oxygen, and structural support essential for their growth (see **Sidebar 9**, p. 46).

Carcinogens can cause cancer in more than one way. While some **directly damage DNA**, others **alter the tissue microenvironment** in ways that promote the growth of cells that are already mutated. Highly mutated cells can remain dormant for long periods but form tumors when exposed to tissue damage, inflammation, or other tumor-promoting conditions.

Source: (190). W18

SIDEBAR 10

Influence of the Gut Microbiome on Cancer Development and Treatment

The gut microbiome consists of all the bacteria, fungi, viruses, and other microorganisms that reside in the digestive tract. These microbes play important roles in digestion, metabolism, immune function, and protection against infection. Research has increasingly shown that the gut microbiome can also influence cancer development and treatment.

Recent studies have shown that certain gut microbes and microbial metabolites influence:

Cancer Development

PROMOTING CHRONIC INFLAMMATION that supports tumor initiation and progression (172).

DAMAGING DNA through microbial toxins that generate cancer-promoting mutations (173,174).

REPROGRAMMING CELLULAR METABOLISM through microbial metabolites that promote tumor growth (175).

SUPPRESSING IMMUNE SURVEILLANCE by altering immune cell activity and inflammatory signaling (176).

REMODELING THE TUMOR MICROENVIRONMENT by reshaping immune, metabolic, and hypoxic conditions within tumors (177).

Cancer Treatment

SURGERY by affecting postoperative recovery and recurrence risk (178,179).

CHEMOTHERAPY by disrupting cellular metabolism and promoting DNA damage to enhance its effectiveness (180).

RADIOTHERAPY by modulating antitumor immune responses and treatment-related toxicities (181).

MOLECULARLY TARGETED THERAPY by altering drug metabolism and immune responses that affect treatment sensitivity and resistance (182).

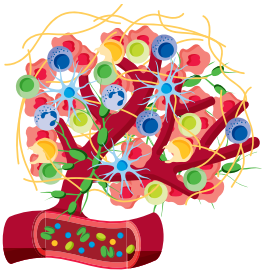
IMMUNOTHERAPY by shaping the activity of immune cells that recognize and attack cancer (183).

Understanding the TME is essential for gaining insights into cancer development and advancing cancer therapies, as it reveals how the surrounding cellular and structural environment supports tumor growth and may be targeted to improve therapeutic outcomes.

Recent advances in single-cell and spatial transcriptomic technologies (see **Sidebar 8**, p. 41) are transforming our understanding of the TME by helping map the cellular and molecular interactions that occur within and around tumors. These technologies can determine how cells organize and communicate across three dimensions within the microenvironment, uncovering evolving processes that promote or suppress tumor growth and metastasis, as well as influence responses to therapy. In a recent study, researchers used multi-omic, single-cell, and spatial profiling to reveal how mutations in the *TP53* gene remodel the TME in lung cancer. They found that these mutations remodel the TME by promoting interactions among cancer cells, immune cells, and stromal cells that support tumor progression and metastasis, while also increasing immune checkpoint signaling that may make tumors more responsive to immunotherapy (191).

Studying the TME in cancers that metastasize to the brain may offer valuable insights into why these tumors are often difficult to treat. Beyond the challenge of delivering drugs across the blood–brain barrier, the brain microenvironment itself can suppress immune responses and provide signals that help metastatic cancer cells survive and resist therapy. To better understand this environment, researchers are using advanced technologies that analyze individual cells and their activity within the tumor's structure. In a recent study, researchers built a comprehensive single-cell atlas of brain metastases across several cancer types, revealing features that help tumors adapt and survive in the brain microenvironment (192). These findings highlight how studying tumor cells and their surroundings can reveal molecular underpinnings of tumor growth and resistance to treatment and may point to new ways to improve therapy.

Metabolic conditions within the tumor microenvironment can influence cancer initiation, progression, and metastasis.



Tumors adapt to nutrient limitation and metabolic stress by rewiring glucose, lipid, amino acid, and fructose metabolism, allowing them to exploit resources within their microenvironment to support continued growth and survival. These metabolic changes can also create vulnerabilities that researchers are exploring as potential therapeutic targets.

Sources: (193-198).

W19

Normal aging is the greatest risk factor for cancer. As tissues age, changes in the TME—including declining immune surveillance, chronic inflammation, and cellular senescence—create tumor-promoting conditions, although some age-related changes have context-dependent effects on cancer initiation and progression. For example, one recent study found that aging can promote metastatic spread by activating stress response pathways that increased lung tumor plasticity and adaptability (199). In contrast, additional studies have shown that aging altered the lung microenvironment in ways that reduced the initiation of *KRAS*-driven lung tumors and also slowed the growth of tumors that did develop by reshaping both cancer cells and their surrounding microenvironment (200,201). Together, these findings highlight how age-related changes in the TME can have both tumor-promoting and tumor-suppressive effects that influence cancer development.

Within the TME, the tumor immune microenvironment (TIME) refers to the network of immune cells and immune-modulating factors that interact with the tumor. The TIME plays an important role in cancer development and response to treatment, and a deeper understanding of these processes is essential for advancing effective immunotherapies.

Emerging research suggests that age-related weakening of the immune system, known as immune aging, makes it harder for the body to detect and eliminate cancer cells and may alter the TIME in ways that support tumor growth and treatment resistance. For example, research has found that age-associated clonal hematopoiesis may contribute to these changes by altering the composition and behavior of tumor-infiltrating immune cells, remodeling the TIME in ways that promote tumor progression and are associated with poorer clinical outcomes (202).

Immune aging is driven by several interconnected biological processes, including chronic inflammation and cellular senescence—a state in which cells permanently stop dividing in response to stress, damage, or aging signals but remain metabolically active. As senescent cells accumulate within aged tissues and secrete pro-inflammatory factors, they weaken immune system function, making it harder for the body to remove both senescent and malignant cells (203). Therapies that target senescent cells, reduce inflammation, or enhance immune activity may reshape the aging TIME and improve clinical outcomes.

Integrating Knowledge to Advance Cancer Research and Precision Medicine

Breakthrough discoveries and technological innovations have significantly advanced our understanding of cancer initiation and progression, enabling the development of a myriad of effective anticancer therapies in recent years (see **Sidebar 11**, p. 51). A crucial insight stemming from this knowledge is the understanding that each patient's cancer is unique.

This understanding has paved the way for precision medicine, also called personalized medicine, which is broadly defined as using information about a person's genes, proteins, environment, and lifestyle to prevent, diagnose, or treat disease (see **Figure 7**, p. 52). For patients with cancer, precision medicine means using molecular characteristics of the tumor, such as the genome sequence of cancer cells or features of the tumor-associated immune cells, to make a diagnosis, plan treatment, and predict and monitor treatment response.

Technological Innovations and Collaborative Science

By leveraging emerging technologies and multi-omic data (see **Sidebar 8**, p. 41), researchers are generating a complete picture of the cellular and molecular characteristics that drive cancer. This comprehensive approach, coupled with powerful computational tools and shared research platforms, is enabling deeper integration of cancer biology insights and driving the development of more personalized therapies, refining tumor classification, revealing novel therapeutic targets, and addressing key challenges such as treatment resistance. For example, by integrating whole-genome sequencing with complementary molecular analyses and clinical data, researchers can identify clinically actionable biomarkers that may be missed by more limited testing approaches and can inform diagnosis, hereditary cancer risk assessment, and treatment selection (204,205).

SIDEBAR 11

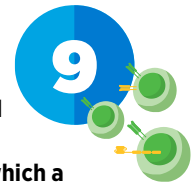
The Therapeutic Impact of Understanding Cancer Biology

A more comprehensive understanding of the genetic and molecular underpinnings of normal and tumor cell biology has led to the development of **more than 200 therapeutics approved by FDA that target specific molecules involved in cancer**.

Advances in understanding that cancers arising in different tissues can be driven by the same molecular biomarkers has led to **9 FDA-approved site-agnostic therapies—such as those targeting *NTRK* gene fusions or HER2 overexpression—marking a shift toward biomarker-driven treatment decisions regardless of tumor origin**.

Identification of the epigenetic factors that influence cancer development has led to **11 FDA-approved therapeutics that work by targeting the proteins that modify the epigenome**.

Knowledge that cancer cells evade immune destruction by exploiting immune checkpoint pathways has led to the development of **15 FDA-approved inhibitors targeting PD-1, PD-L1, CTLA-4, and LAG-3 immune checkpoints**.



A deeper understanding of how T cells can be harnessed to fight cancer has led to the development of **9 FDA-approved adoptive T-cell therapies—including CAR T-cell, TIL, and TCR T-cell therapies—in which a patient's own T cells are modified to enhance their cancer-fighting capabilities**.

CAR, chimeric antigen receptor; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

Researchers have recently developed **AlphaGenome, an AI model that can predict how genetic variants alter gene activity, chromatin structure, and RNA processing**—providing new insights into the molecular mechanisms that drive cancer and other diseases.

Source: (212).

W20

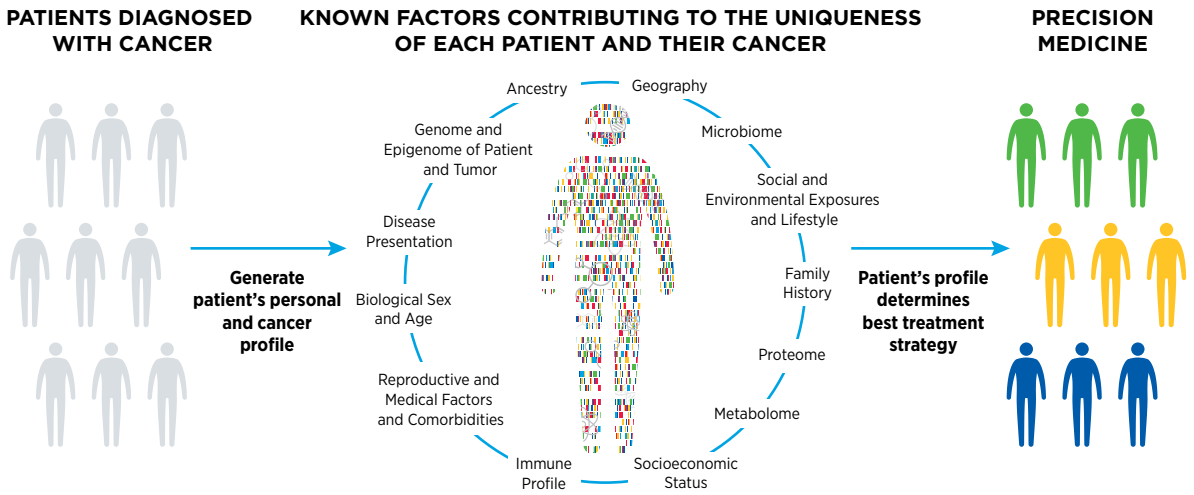
These advances are increasingly being implemented through large-scale precision medicine initiatives that integrate genomic and clinical data across populations. National programs such as Germany's genomDE strategy, Finland's FinnGen project, and the Taiwan Precision Medicine Initiative are creating extensive genomic and health data resources that support biomarker identification, risk prediction, and the development of more personalized approaches to prevention, diagnosis, and treatment (206-208).

AI and advanced computational approaches are becoming essential tools for translating the growing volume of biological and clinical data into actionable insights that can guide precision oncology. Recent advances have highlighted the ability of AI-driven approaches to integrate diverse datasets, improve patient stratification, predict treatment response, and accelerate the development of new therapies (209,210). Reflecting the increasing importance of AI-driven approaches in cancer research, an executive order issued in September 2025 directed federal agencies to expand the use of AI in pediatric cancer research through the Childhood Cancer Data Initiative. This order emphasized leveraging large-scale health and research data resources to improve cancer diagnosis, biomarker discovery, clinical trial design, treatment development, and prevention strategies (see **Improving the Use of Digital Information in Cancer Treatment and Management**, p. 201) (211).

Large-scale data-sharing initiatives, such as The Cancer Genome Atlas (TCGA) and the Cancer Dependency Map (DepMap), have laid the groundwork for a more comprehensive understanding of cancer biology. TCGA has enabled an extensive catalog of genetic, epigenetic, and molecular changes, or "maps," across patient tumors, thus providing a reference point for distinguishing tumor subtypes and identifying common oncogenic pathways. DepMap has complemented this effort by providing a large-scale data repository for genetic and molecular vulnerabilities, or weak points that cancer cells rely on for survival, across a wide array of cancer models routinely used by researchers (see **Sidebar 4**, p. 33). In April 2026, DepMap announced the launch of its next phase, which aims to accelerate the discovery of emerging therapeutic modalities while advancing efforts to overcome therapeutic resistance (213).

Building on these foundational resources, the Human Tumor Atlas Network (HTAN), a collaborative, data-

FIGURE 7
Precision Medicine



Precision medicine, also called personalized medicine, is broadly defined as using information about a person's genes, proteins, environment, and lifestyle to prevent, diagnose, or treat disease. The factors that contribute to the uniqueness of a patient and the patient's cancer include, but are not limited to, the person's inherited and tumor's genome, epigenome, transcriptome, proteome, microbiome, and metabolome, the immune characteristics of the person and the cancer, disease presentation, biological sex, ancestry, social and environmental exposures, lifestyle, and comorbidities.

Currently, genomics is the predominant factor influencing precision medicine, but additional factors, such as epigenomics, tumor immune characteristics, microbiome, and so on, are further refining personalized approaches to cancer care. Assessment of the proteome also plays a critical role in precision medicine, including through biomarkers such as estrogen receptor expression in breast cancer. Although genomic profiling of a patient and of the patient's tumor is becoming routine in the clinic, stark disparities exist in the utilization of these services, with lower uptake among medically underserved populations.

intensive cancer research initiative launched as part of the Cancer Moonshot, is applying advanced technologies to study individual cells and their molecular features within the structure of tumors. HTAN studies use single-cell, spatial, and multi-omic technologies (see **Sidebar 8**, p. 41)—including genomic, transcriptomic, proteomic, and advanced imaging approaches—to map the cellular and molecular architecture of tumors and premalignant tissues across disease initiation, progression, and metastasis (214-217). As of June 2026, HTAN investigators have generated 14 tumor atlases spanning 20 organ sites, providing a resource empowering researchers across the globe to decode the cellular and molecular complexity of cancer at unprecedented resolution (218).

Beyond generating data resources, international collaborative research initiatives, such as the Cancer Grand Challenges, are applying integrative approaches to tackle some of cancer's most complex and unresolved questions. Launched as a global partnership between the National Cancer Institute and Cancer Research UK, Cancer Grand Challenges brings together multidisciplinary teams from around the world to tackle scientific challenges that are too complex for any single laboratory or institution to address (see **Sidebar 12**, p. 53).

These challenges focus on critical unmet needs that demand integrated research spanning cancer biology, environmental exposures, and social drivers of health, such as determining the cause of early-onset cancers; understanding the biology of ecDNA and the dark proteome; addressing cancer cachexia (see **Challenges Faced by Survivors**, p. 145); developing novel therapies for pediatric cancers; addressing cancer inequities; and uncovering the dynamic interactions between the nervous system and cancer. By supporting bold, collaborative science that spans basic, translational, clinical, and population-based research, this initiative highlights the importance of integrating knowledge across domains to advance cancer prevention, detection, and treatment for all patients.

SIDEBAR 12

Cancer Grand Challenges

Cancer Grand Challenges is a global initiative co-founded in 2020 by NCI and Cancer Research UK (CRUK), building on CRUK's Grand Challenge initiative established in 2015, to address some of the most complex and pressing scientific challenges in cancer research. The program fosters international collaboration by funding large, multidisciplinary teams working across basic, translational, clinical, and population-based science to improve outcomes for cancer patients.

SCOPE: Challenges are designed to tackle questions that no single team or institution could solve alone, spanning cancer biology, environmental exposures, and social drivers of health.

FUNDING: Each funded team receives up to $25 million to pursue high-risk, high-reward research. Funding rounds occur approximately every 2 years, with teams selected through a competitive, expert-reviewed process.

Recently Funded Challenges

In March 2025, new challenges were announced—these represent urgent, complex problems in cancer research. In March 2026, five international teams were selected to address these challenges (219).

CANCER AVOIDANCE: Discover why some people who are at high risk, such as those with cancer-causing mutations or those who live to old age, manage to avoid developing cancer.

Team ATLAS will explore how autoantibodies, which are antibodies made by the immune system that mistakenly target the body's own cells or tissues instead of harmful pathogens, may help certain high-risk individuals avoid developing cancer by studying unique populations—including centenarians, cancer-resistant individuals with high-risk exposures, and twins discordant for cancer—to identify protective immune mechanisms, biomarkers, and potential prevention strategies.

THE DARK PROTEOME: Explore proteins that remain poorly understood—often because they are made from unknown genetic instructions or have unexpected modifications not explained by changes in DNA—to see how they influence cancer and whether they could lead to new treatments.

Team ILLUMINE will create a comprehensive atlas of the cancer dark proteome to uncover how mysterious proteins and peptides—generated from unconventional genetic instructions or unexpected modifications—drive cancer progression and can be targeted with next-generation immunotherapies for hard-to-treat cancers.

MECHANISMS DRIVING MUTATIONAL SIGNATURES: Uncover the cause of unexplained DNA damage patterns, or "mutational signatures," found in cancer cells to inform cancer prevention measures.

Team CAUSE will develop advanced experimental and artificial intelligence–driven tools to identify and characterize DNA adducts—chemical modifications that form when carcinogenic molecules bind to DNA—and link specific DNA damage patterns to their underlying biological or environmental causes, ultimately informing cancer prevention strategies.

THE NERVOUS SYSTEM AND CANCER: Investigate how the nervous system and cancer cells communicate with each other and how this relationship might influence cancer growth, spread, and treatment response.

Team InteroCANCEption will investigate how bidirectional communication between the brain, nervous system, and tumors influences cancer growth, metastasis, immune and metabolic responses, and treatment outcomes, with the goal of developing targeted neuromodulation therapies to improve patient care.

REWIRING CANCER CELLS: Find innovative ways to change the signaling systems of cancer cells so that they behave less aggressively or become more vulnerable to treatment.

Team REWIRE-CAN will reprogram colorectal cancer cells into vulnerable or treatment-sensitive states by disrupting their finely balanced signaling networks through hyperactivation, cell-state reprogramming, and strategies that prevent the development of treatment resistance.

Previously funded challenges continue to support international teams tackling topics including cancer inequities, early-onset cancers, solid tumors in children, T-cell receptors, cachexia, extrachromosomal DNA, normal phenotypes, and microbiota. By enabling innovative, cross-disciplinary science, Cancer Grand Challenges is redefining how the global research community tackles the most formidable barriers to progress across the cancer continuum. In March 2027, the next set of new challenges will be announced.

As precision oncology advances, it is essential to ensure that its benefits are accessible to all patients. Researchers have recently emphasized the need to diversify genomic datasets and include ancestral and environmental variables in both research and clinical implementation (220). Moving forward, broadening representation in studies and making molecular testing and new treatments more accessible across patient populations will be essential to realizing the full potential of precision medicine for all patients (see **Progress Across the Clinical Cancer Care Continuum**, p. 98).

Reducing the Risk of Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- In the United States (US), 40 percent of all cancer cases are attributable to modifiable risk factors.
- Use of tobacco products has declined substantially in the United States, with adult cigarette smoking prevalence falling to single digits for the first time in 2024.
- Any level of alcohol consumption can increase the risk of cancer development.
- Excess body weight, physical inactivity, and poor diet are associated with approximately 20 percent of all cancers diagnosed in the United States.
- Weight loss interventions, including bariatric surgery and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), can reduce the risk of developing obesity-related cancers.
- Vaccination against human papillomavirus (HPV) can nearly eliminate the risk of HPV-associated cervical, vulvar, penile, and anal cancers.
- The US Food and Drug Administration (FDA) recently approved the use of bemotrizinol in sunscreens. Bemotrizinol is the first new active ingredient approved by FDA for over-the-counter sunscreens since the late 1990s.

Progress across basic, clinical, translational, and population sciences has substantially improved the understanding of factors that influence cancer risk (see **Figure 8**, p. 56). In the United States (US), approximately 40 percent of new cancer cases diagnosed in 2019 were linked to modifiable risk factors, including tobacco use, ultraviolet (UV) radiation exposure, excess body weight, alcohol consumption, physical inactivity, and certain infections (221). In 2023, approximately 42 percent of all cancer-related deaths, globally, were attributed to tobacco use, alcohol consumption, infectious agents, and excess body fat (222). Because many of these factors can be modified, a meaningful share of cancer cases may be preventable through targeted risk-reduction strategies.

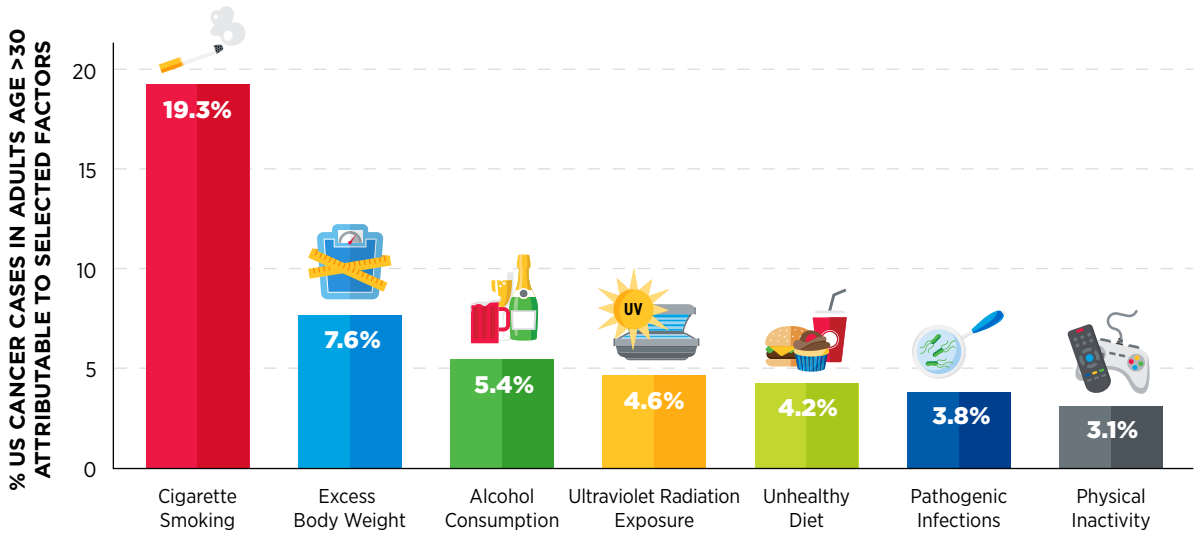
These modifiable risk factors are shaped by broader social and structural conditions (see **Figure 2**, p. 22), which can limit the effectiveness of individual behavioral changes alone. For instance, limited access to affordable, nutritious food can make it difficult to maintain a healthy diet, and neighborhood conditions—such as safety and availability of recreational spaces—can influence opportunities for physical activity. Reducing exposure to modifiable risk factors, and ultimately the overall burden of cancer, will likely require a combination of individual-level interventions and broader environmental and policy approaches.

In the United States, substantial declines in cancer morbidity and mortality have been driven by effective public health education and policy efforts. An analysis by the National Cancer Institute (NCI) estimated that approximately 5.94 million cancer deaths were prevented between 1975 and 2020 as a result of interventions such as tobacco control, population-based screening, vaccination programs, and advances in treatment (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 189). These improvements have been most pronounced for cancers with established screening approaches, including breast, cervical, colorectal, and prostate cancers (see **Cancer Screening for Early Detection**, p. 82). Reductions in lung cancer mortality accounted for the largest share of deaths averted, largely reflecting the impact of tobacco control initiatives (224).

Despite this progress, the growing prevalence of other risk factors—such as obesity among both children and adults and alcohol use among adults—continues to pose challenges for cancer prevention. In 2024, 85 percent of

FIGURE 8

Modifiable Cancer Risks



Research has identified numerous factors that increase an individual's risk for developing cancer. By modifying behavior and reducing environmental exposures, individuals can reduce or eliminate many of these risks and thereby lower their risk of developing or dying from cancer. Developing and implementing additional public health interventions that are based on rigorous scientific approaches in lock step with policy initiatives can help further reduce the burden of cancers related to modifiable risk factors.

Sources: (221,223).

US adults age 18 and older reported consuming alcohol at some point in their lives (225). In addition, many preventive measures remain underused, including vaccination against cancer-related infections. For example, coverage of the human papillomavirus (HPV) vaccine—an effective tool for preventing cervical and certain head and neck cancers—remains suboptimal. At the same time, ongoing research is examining how emerging factors, such as climate change, environmental contaminants, occupational exposures, and disruptions to sleep and circadian rhythms, may influence cancer risk (see **Sidebar 13**, p. 57).

Harmful contaminants found in air and drinking water, including arsenic, nitrates, disinfection byproducts, and per- and polyfluoroalkyl substances (PFAS), have been linked to elevated cancer risk (238,239). In addition, occupational exposures to hazardous agents—such as chemicals encountered during firefighting, silica dust in mining, and noxious fumes in fabrication or roofing—can significantly contribute to cancer development.

Emerging evidence suggests that certain cancer risk factors are also associated with worse outcomes after a cancer diagnosis, including the risk of developing second primary cancers (see **Advancing Cancer Survivorship Care**, p. 144). In addition, many cancer risk factors are linked to other chronic conditions, including cardiovascular disease, respiratory illness, and diabetes. Greater awareness of these modifiable risks can support more effective prevention strategies and help reduce the broader health and economic burden associated with cancer and other chronic diseases.

Eliminate Tobacco Use

Tobacco use remains the foremost preventable cause of cancer and is associated with the development of at least 17 cancer types (see **Figure 9**, p. 58). In the United States, cigarette smoking is responsible for more than 19 percent of all cancer cases and nearly 30 percent of cancer-related deaths (221). Smoking also accounts for the vast majority of lung cancer cases and deaths. In 2019, the most recent year for which data are available, smoking accounted for an estimated 87 percent of lung cancer cases in men and 84 percent in women (221).

SIDEBAR 13

Emerging Cancer Risks

Emerging risk factors are those whose potential impacts on cancer risk and outcomes are still evolving but may have substantial public health implications.

Climate change

Climate change refers to long-term changes in Earth's temperatures and weather patterns. It is increasingly recognized as a cross-cutting threat that can influence environmental and occupational exposures—including exposure to hazardous chemicals such as per- and polyfluoroalkyl substances (PFAS)—while also affecting workers through heat, wildfire smoke, and other climate-related hazards. Climate change may further disrupt the cancer care continuum by affecting access to prevention, screening, diagnosis, treatment, and survivorship care, highlighting the need for continued research and preparedness. For example, in Europe, low-income households are 10.9 percent more likely than middle-income households to experience food insecurity, a social driver of health associated with increased cancer risk and poorer cancer outcomes, as heatwave and drought events become more frequent and severe (226-228).

Per- and polyfluoroalkyl substances, "the forever chemicals"

A large study linked PFAS contamination in drinking water to increased incidence of multiple cancers, including cancers of the endocrine, digestive, respiratory, and urinary systems, as well as leukemia and brain cancer (229).

Firefighter occupational exposures

Firefighters are exposed to numerous known and suspected carcinogens, including combustion products, diesel exhaust, asbestos, and PFAS. Occupational exposure as a firefighter is classified as carcinogenic to humans and is associated with increased risks of mesothelioma and bladder cancer, with suggestive evidence for several other cancers (230).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

Among individuals who are obese or overweight, GLP-1 RA use was associated with a potential increase in kidney cancer risk that warrants further investigation, although it was also linked to a lower overall cancer risk and reduced risks of endometrial, ovarian, and meningioma cancers (231).

Endocrine-disrupting chemicals and other carcinogens in hair products

Recent evidence linking chemical hair relaxer use to increased cancer risk has prompted women to adopt alternative hair-styling practices. However, concerns have emerged regarding some braiding hair products, which have been found to contain heavy metals and other potentially hazardous chemicals, raising concerns that avoiding one potentially harmful exposure could inadvertently introduce another. These findings underscore the need to systematically evaluate the chemical safety of alternative hair products and the health implications of shifting exposure profiles (232-234).

Circadian rhythm disruption and poor sleep

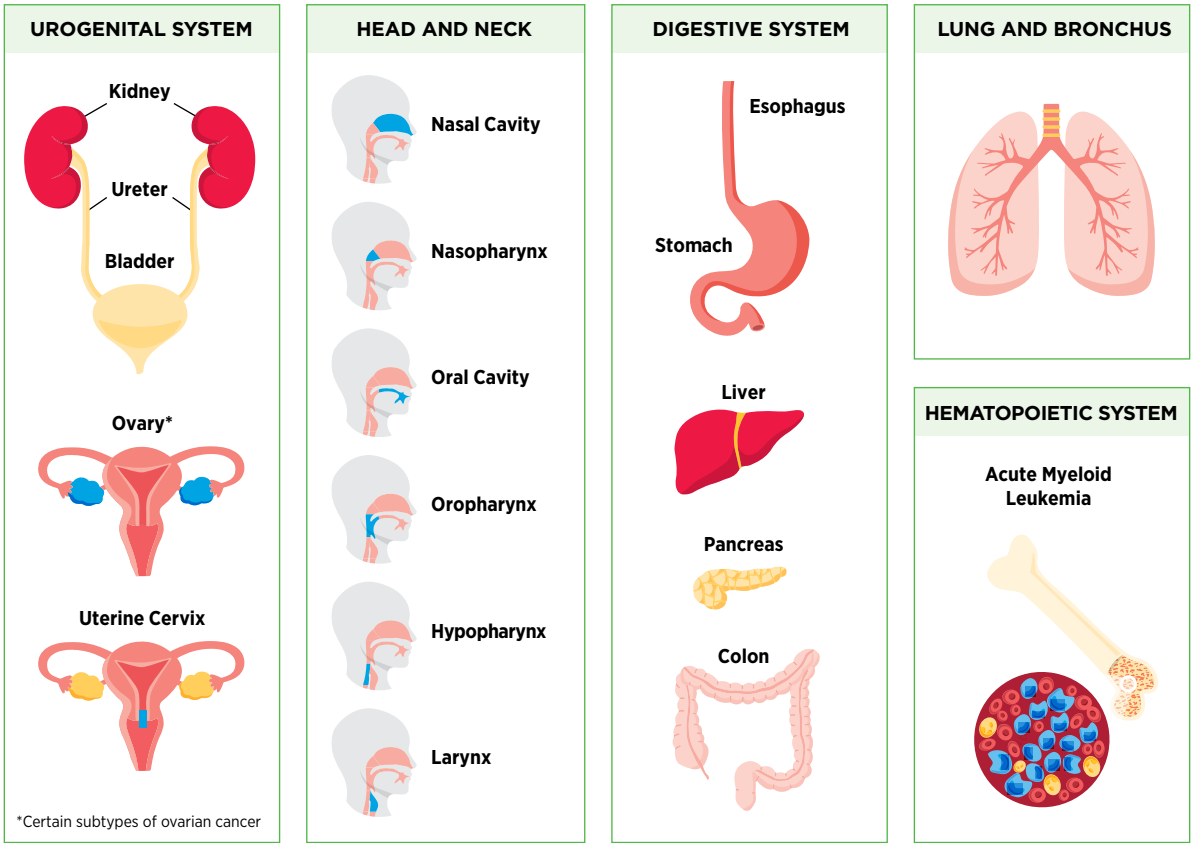
Disruption of circadian rhythm has long been associated with an increased risk of cancer development, and the International Agency for Research on Cancer has classified night-shift work as a possible carcinogen. Insomnia has also been associated with an increased risk of early-onset hormone-related cancers, including breast, uterine, and ovarian cancers. In addition, poor sleep health has been linked to more aggressive breast cancer in Black women, a higher risk of breast cancer among Asian and Hispanic women, and an increased risk of overall cancer development in Hispanic individuals (235-237).

Research conducted over the past five decades has established that exposure to carcinogenic compounds generated by the use of tobacco products, including cigarettes, can induce lasting cellular and molecular damage that contributes to cancer development (240-242). In the United States, more than 16 million adults are living with chronic health conditions attributable to tobacco use, including chronic obstructive pulmonary disease (COPD), asthma, a range of cardiovascular diseases, particularly coronary artery disease, and cancer (243).

National tobacco control policies and programs have been instrumental in lowering tobacco use in the United States and

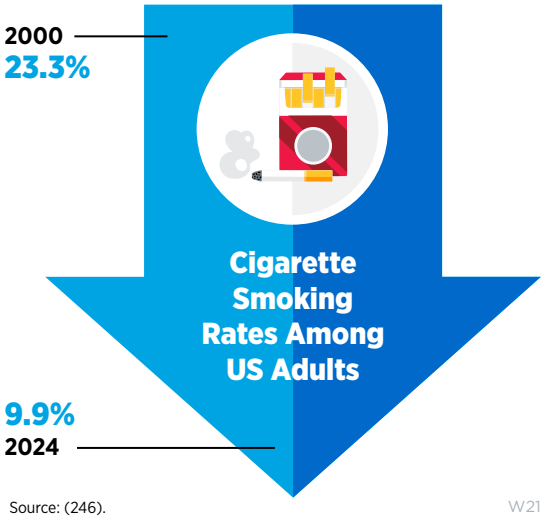
FIGURE 9

Beyond the Lungs: Cancers Caused by Tobacco Use



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 cancers.

Sources: (221,223).



Source: (246).

W21

mitigating the public health burden associated with smoking. Adult cigarette smoking prevalence declined from 42.4 percent in 1965 to 9.9 percent in 2024 (51). Reaching single-digit smoking prevalence for the first time marks a notable public health achievement and suggests that the Healthy People 2030 initiative—public health priorities established each decade to help individuals, organizations, and communities across the United States improve health and well-being—objective of reducing smoking prevalence to 6.1 percent may be attainable (244). Nevertheless, the decline in cigarette use has coincided with an increase in electronic cigarette (e-cigarette) use among adults. In 2024, an estimated 7 percent of US adults used e-cigarettes (51,245). In addition, approximately 47.7 million adults reported using any tobacco product in 2024, including cigarettes, cigars, and smokeless tobacco products, based on the most recent available estimates (51).

Similar to the trend in adults, tobacco use among US youth—including middle and high school students—is also declining. In 2025, 4.1 percent of middle and 9.5 percent of high school students reported current use of any tobacco product, down from 5.4 percent and 10.1 percent, respectively, in 2024 (247,248).

Marked disparities in tobacco use and exposure to secondhand smoke (SHS), which is also a risk factor for cancer, continue to affect certain population groups, as described in the *AACR Cancer Disparities Progress Report 2026*. Tobacco use prevalence is particularly high among individuals working in primary extractive (29.4 percent) and construction/manufacturing (28.6 percent) occupations, those with a GED certificate (42.8 percent), people with disabilities (21.5 percent), low-income individuals (24.4 percent), and residents of rural communities (27.0 percent) (51). In addition, men report higher tobacco use than women (24.1 percent vs. 13.9 percent) (51).

Flavored tobacco products, particularly menthol cigarettes, pose a substantial public health concern. Compared to non-menthol cigarettes, menthol cigarettes are associated with greater nicotine dependence, lower smoking cessation rates, and higher mortality risk (249-251). In 2021, menthol cigarettes accounted for 37 percent of all cigarette sales in the United States, the highest proportion recorded since major tobacco companies began reporting these data to the federal government in 1963 when menthol cigarettes represented just 16 percent of total US cigarette sales (252).

In 2022, the US Food and Drug Administration (FDA) proposed product standards to prohibit the manufacture and sale of menthol cigarettes and flavored cigars. Because these regulations targeted industry practices rather than individual purchasing or use, they were expected to advance health equity. A recent study estimated that a menthol cigarette ban could save approximately 255,000 Black lives in the United States over 40 years (254). However, FDA withdrew both proposed rules in early 2025 (255). Prior to the withdrawal, tobacco companies conducted direct-to-consumer campaigns encouraging tobacco users to oppose the proposed regulations. Marketing messages used phrases such as "speak your voice," "take action," and "don't stay silent," creating a sense of urgency and framing the proposed bans as unjust restrictions (255).

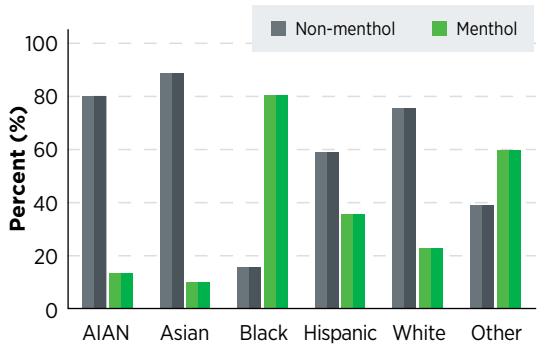
Although smoking prevalence in the United States has declined significantly, cessation remains a challenge. In 2022, 67.7 percent of current smokers expressed a desire to stop, and 53.3 percent attempted to quit, yet only 8.8 percent were successful (256). Smoking cessation provides substantial health benefits, particularly when achieved at younger ages. Compared to people who never smoked, individuals who continue smoking from adulthood lose an average of 9.1, 8.3, 7.3, 5.9, and 4.4 years of life when assessed at ages 35, 45, 55, 65, and 75 years, respectively. Quitting at those same ages reduces the average years of life lost to 1.1, 2.7, 3.9, 4.2, and 3.7 years, respectively, demonstrating the considerable gains in life expectancy associated with smoking cessation (257).

Cigarette Smoking in the United States (2024)

CURRENT SMOKERS BY RACE AND ETHNICITY

21%	AIAN	**8%**	Other
11%	White	**7%**	Hispanic
11%	Black	**4%**	Asian

TYPE OF CIGARETTE SMOKED

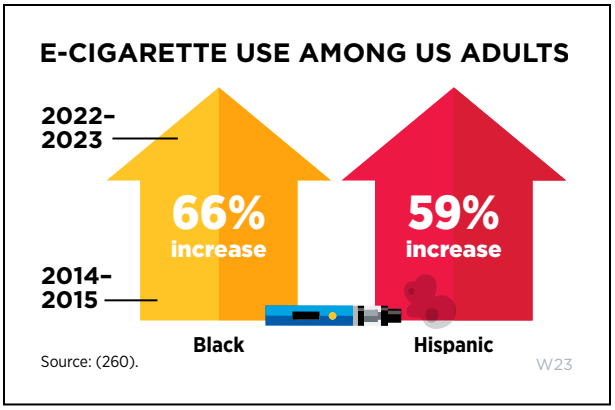


AIAN, American Indian or Alaska Native.
Source: (253).

W22

SHS—the combination of smoke exhaled by tobacco users and smoke emitted from burning tobacco products—contains more than 7,000 chemicals, including at least 70 known carcinogens (258). During 2015–2018, 20.8 percent of nonsmoking US adults age 18 and older were exposed to SHS, as measured by blood cotinine levels. Exposure was disproportionately higher among socioeconomically disadvantaged populations. SHS exposure was 16.8 percent among adults with some college education or more, compared to 29.5 percent among high school graduates and 27.3 percent among those with less than a high school education. Exposure also declined with increasing income: 35.1 percent of adults living below the federal poverty level were exposed to SHS, compared to 11.8 percent of those living at or above 400 percent of the federal poverty level (259).

E-cigarettes were first introduced in the United States in 2006 and have gained popularity, particularly among individuals who have never previously used tobacco products. Since 2014, e-cigarettes have been the most used tobacco product among middle and high school students (247). Although e-cigarettes remains the most commonly used tobacco product among US middle and high school students, prevalence decreased from 9.4



percent in 2022 to 5.2 percent in 2025, representing an average annual decline of 18.1 percent. The decline in current e-cigarette use was most pronounced among high school students, with prevalence falling from 14.1 percent to 7.1 percent during the same period, an average annual decrease of 20.5 percent (248).

Among adults, recent estimates show that e-cigarette use is highest among individuals ages 18 to 24 years, with 14.8 percent reporting current use compared to 3.4 percent reporting regular cigarette use. E-cigarette use is also more prevalent than regular cigarette use among individuals who are single or never married (10.9 percent vs. 8.6 percent), lesbian or gay individuals (19.3 percent vs. 10.6 percent), and those employed in the education sector (4.1 percent vs. 3.7 percent) (51).

The growing use of e-cigarettes poses an important public health concern, as their relationship with cancer risk is not yet fully understood. While e-cigarettes emit fewer carcinogens than combustible tobacco, they still expose individuals to many toxic chemicals, including metals that can damage DNA and trigger inflammation (262,263). Recent reviews suggest that chemicals released by e-cigarette use may be carcinogenic and could increase the risk of lung, bladder, and other cancers (264,265).

Evidence is also emerging regarding the implications of e-cigarette use for lung cancer risk. A recent study of nearly 5,000 newly diagnosed lung cancer cases found that individuals who both vaped and chronically smoked cigarettes had approximately four-fold higher odds of lung cancer compared to those who smoked cigarettes alone (266). Importantly, individuals who switch to e-cigarettes after quitting traditional cigarettes may continue to face an elevated risk of lung cancer.

IN CALIFORNIA, FLAVORED TOBACCO BANS
REDUCED THE USE OF ELECTRONIC VAPING PRODUCTS AMONG YOUTH
BY 2.4 PERCENTAGE POINTS BETWEEN 2017 AND 2022

Source: (261). W24

Compared to former smokers who did not use e-cigarettes, those who used e-cigarettes after smoking cessation had a 56 percent higher risk of developing lung cancer and a two-fold higher risk of lung cancer–specific mortality (267). These findings suggest that continued e-cigarette use after smoking cessation may diminish some of the cancer-related health benefits associated with complete smoking cessation.

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

In 2019, an estimated 15 percent of new cancer cases and 14 percent of cancer deaths among US adults were attributable to the combined effects of excess body weight, poor diet, and physical inactivity (see **Figure 10**, p. 61) (221). Maintaining healthy body weight, engaging in regular physical activity, and following a balanced diet can help reduce the risk of cancer as well as other chronic diseases (see **Sidebar 14**, p. 62). Beyond its contribution to cancer risk, a high body mass index (BMI) has emerged as one of the leading contributors to reduced life expectancy in the United States, ranking among the top five risk factors over the past decade (268).

Excess body weight alone accounts for 7.6 percent of all cancer cases (221). In 2024, an estimated 33.7 percent of US adults age 18 and older were overweight and 33.4 percent were obese (253,269).

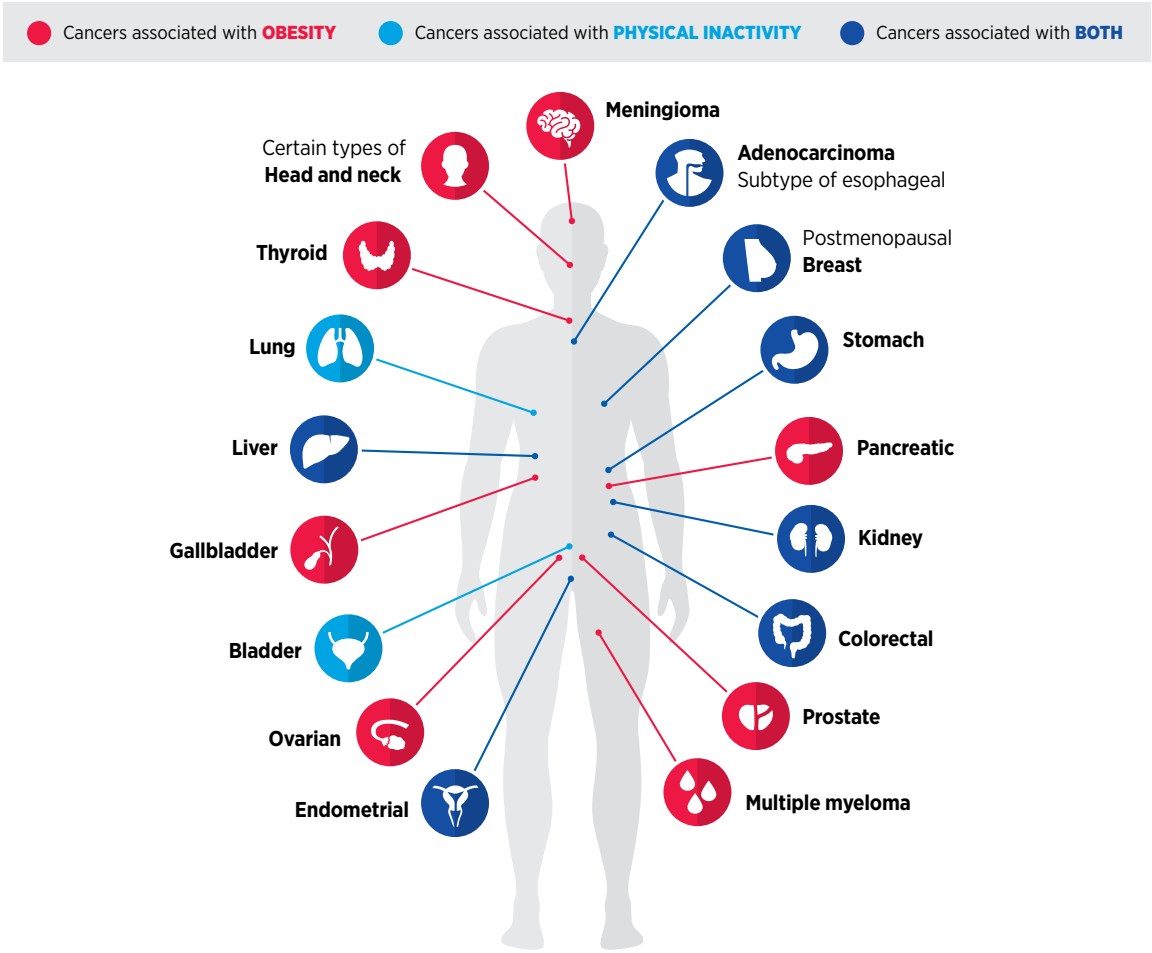
Obesity is also prevalent among US youth. In 2024, a nationally representative study found that 19.8 percent of individuals ages 2 to 19 years were obese. The prevalence of overweight or obesity increased with age, from 26.9 percent among children ages 2 to 5 years to 38.5 percent among adolescents and young adults ages 12 to 19 years. Severe obesity affected 9.2 percent of adolescents and young adults (277). Importantly, the impact of obesity during these formative years extends into adulthood. Childhood and adolescent obesity has been associated with a 33 percent higher risk of developing cancer and a 28 percent higher risk of cancer-related mortality later in life (278).

As body weight increases, organs often enlarge to meet the metabolic demands of maintaining a larger body and the body's normal functions. Emerging evidence suggests that this increase in organ size may contribute to cancer risk. A recent study reported significant associations between the size of the liver, pancreas, and kidneys and cancer risk, finding that a doubling in organ size was associated with approximately a doubling in cancer risk (279).

Obesity is also a growing global public health challenge. According to the World Health Organization (WHO),

FIGURE 10

Reasons to Maintain a Healthy Weight and Stay Physically 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 breast (postmenopausal), colon, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, rectal, stomach, and thyroid cancers—have all been directly linked to being overweight or obese. Being physically active lowers the risk of nine types of cancer—bladder, breast (postmenopausal), colon, endometrial, esophageal, kidney, liver, lung, and stomach cancers. 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 inactivity are shown in light blue; cancers associated with both are shown in dark blue.

Sources: (223,270-276).

43 percent of adults worldwide were overweight and 16 percent were obese in 2022, the most recent year for which global estimates are available (280). Childhood obesity is also increasing globally. In 2024, 8 percent of children and adolescents were obese, compared to 2 percent in 1990. Looking ahead, projections suggest that by 2030 nearly three billion adults—approximately 50 percent of the world's adult population—will have a BMI greater than 25 kg/m^2 (281).

Recognizing the urgency of the obesity crisis, WHO Member States endorsed the WHO Acceleration Plan to Stop Obesity at the 2022 World Health Assembly. Building on this

SIDEBAR 14

Ways to Reduce Cancer Risk

Research shows that approximately 40 percent of all cancers diagnosed in the United States are attributable to modifiable lifestyle factors. Lifestyles, behaviors, and exposures are strongly influenced by living environments. These living environments create barriers to behaviors that are important in lowering cancer risk. It is imperative that all sectors work together to identify more effective strategies for reducing these barriers to healthy behaviors, disseminating our current knowledge of cancer prevention, and implementing evidence-based interventions to reduce the burden of cancer risks for everyone. Based on current evidence, public health experts recommend that people*:

Maintain a healthy weight. 15 types of cancer have been causally linked to being obese or overweight.†

Be physically active. Regular physical activity can decrease risk for nine types of cancer.

Eat at least 30 grams of fiber and at least 400 grams of fruit and vegetables daily. A diet rich in vegetables, fruits, whole grains, and beans provides naturally occurring nutrients that help combat inflammation triggered by environmental exposures and other factors linked to increased cancer risk.

Get vaccinated. Vaccines against cancer-causing pathogens such as HPV and HBV are available.

Breastfeed after pregnancy. For mothers, (if feasible), breastfeeding can reduce breast cancer risk.

Do not use tobacco products (e.g., cigarettes, e-cigarettes, and chewing tobacco).

Limit consumption of "fast foods" and other processed foods. Foods high in fat, simple starches, or added sugars contribute to weight gain while providing little nutritional value.

Limit intake of red meat (e.g., beef, pork, and lamb) to no more than three servings a week (12 to 18 ounces a week) and **consume very little or avoid processed meats** (e.g., hot dogs, bacon, and salami) as these foods are associated with an increased risk of colorectal and other cancers.

Limit alcoholic drinks (if consumed at all). Alcohol consumption can increase risk for seven types of cancer.

Limit sun exposure. Limit even on cloudy days, and wear sunscreen with SPF 30 or higher.

HBV, hepatitis B virus; HPV, human papillomavirus.

* Greater adherence to recommendations pertaining to diet and physical activity have been shown to be associated with a reduced risk of all-cause, cancer-specific, and cardiovascular disease–related mortality among adults ages 50 to 71 (288).

† Overweight and obesity are often assessed using body mass index (BMI): BMI between 18.5 kg/m^2 and 24.9 kg/m^2 is considered healthy weight. However, it must be noted that the use of BMI has limitations, as it is not an accurate measure of obesity or body fatness for all individuals. Researchers are currently investigating novel biomarkers that are better indicators of body fatness and predictive of cancer risk.

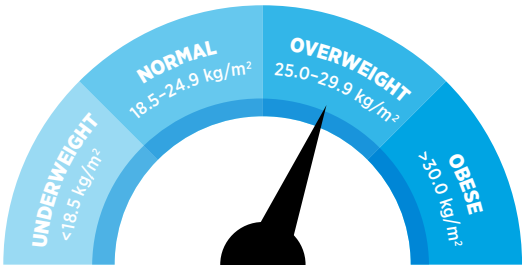
Source: (289).

effort, WHO released the Adopt, Create, and Transform (ACT) technical package in 2025 to support governments and other stakeholders in implementing evidence-based strategies aimed at reducing obesity prevalence by 5 percent by 2030 (287). The ACT framework focuses on promoting environments that support healthy diets and active living; strengthening knowledge, motivation, and skills for healthy behaviors; and transforming health systems to better prevent and manage obesity.

Data show that weight loss interventions (see **Sidebar 15**, p. 64) can be effective in reducing the risk of cancers associated with obesity (290). Bariatric surgery is a collection of procedures that when effectively paired with healthy eating and regular exercise may help people who are obese lose weight. Bariatric surgery has also been shown to lower the risk of developing and/or dying from certain obesity-related cancers by between 37 percent and 65 percent (291). These include cancers of the liver, colon, pancreas,

BMI and Obesity

Body mass index (BMI), which is calculated as weight in kilograms divided by height in meters squared, is used as an indirect measure of body fat and to define healthy weight, overweight, and obesity. In adults:



Obesity has 3 classifications:

- **Class I:** 30.0–34.9 kg/m²
- **Class II:** 35.0–39.9 kg/m²
- **Class III:** ≥40.0 kg/m²

BMI has historically been used to measure obesity because it is easier to calculate. However, BMI has limitations, as it does not account for muscle mass or sarcopenic obesity; therefore, it may over- or underestimate body fat for certain individuals including older adults and those who are Black or Asian. Recently, a global group of experts proposed a broader definition of clinical obesity—one that goes beyond just body weight or BMI—by considering factors that reflect the specific effect of obesity, such as reduced organ or tissue function and limitations of daily activities. The updated definition includes how excess body fat affects the body's organs and interferes with a person's ability to carry out everyday activities.

Sources: (282-286). W25

and gallbladder, as well as breast, endometrial, and ovarian cancers in women (291).

Another increasingly common approach to weight loss is the use of medications such as semaglutide (e.g., Ozempic, Wegovy, and Rybelsus), liraglutide (e.g., Victoza), and tirzepatide (e.g., Mounjaro and Zepbound), which were initially developed to treat type 2 diabetes mellitus (T2DM).

GLP-1 receptor agonist use was associated with a **32% lower chance** of **developing breast cancer**.

Source: (293). W26

These medications belong to a class of drugs known as glucagon-like peptide-1 receptor agonists (GLP-1 RAs). They mimic the actions of GLP-1, a naturally occurring hormone that regulates blood glucose levels, suppresses appetite, and promotes satiety after eating (292).

The use of GLP-1 RA–based therapies has increased rapidly in the United States, prompting interest in their potential effects on cancer risk. However, evidence regarding their impact on obesity-related cancers remains mixed and varies by type of GLP-1 RA used (294,295).

Recent studies suggest that some GLP-1 RAs may reduce the risk of certain obesity-related cancers. For example, a United Kingdom study found that semaglutide use was associated with a 12 percent reduction in obesity-related cancer risk, compared to a 15 percent reduction among individuals undergoing bariatric surgery. In the same study, tirzepatide was not associated with a significant reduction in overall obesity-related cancer risk, although it was linked to a 69 percent lower risk of ovarian cancer (290). Similarly, among individuals with T2DM, GLP-1 RA use was associated with a 40 percent and 46 percent lower risk of esophageal and colorectal cancer, respectively, compared to insulin therapy (296).

Additional evidence indicates that GLP-1 RA use may be associated with reductions in the risk of several obesity-related cancers, including gastrointestinal, skin, breast, female genital, prostate, and hematologic cancers, with reported risk reductions ranging from 18 percent to 38 percent. Among individual agents, semaglutide demonstrated particularly strong protection against gastrointestinal cancers, reducing risk by 55 percent. In contrast, liraglutide use was associated with increased risks of thyroid and respiratory cancers, by 70 percent and 62 percent, respectively (297).

Despite these findings, evidence remains inconsistent. A review of 48 clinical trials involving more than 94,000 participants treated with GLP-1 RAs found no significant reduction in the overall risk of obesity-related cancers (298). Taken together, the current literature suggests that while GLP-1 RA–based therapies are effective for weight loss and metabolic control, their role in cancer prevention remains uncertain and warrants further investigation.

While the observational studies discussed above suggest that GLP-1 RA use may influence cancer risk, their findings remain

SIDEBAR 15

Interventions to Reduce Obesity

In 2024, an estimated 33.4 percent of US adults 18 and older were considered obese. In addition to cancer, being overweight or obese can increase the risk of hypertension, type 2 diabetes mellitus (T2DM), coronary heart disease, and stroke. Alongside promoting healthy eating and increased physical activity, individuals may be offered surgical and medication-based therapies to help address chronic obesity.

Bariatric Surgery

A collection of surgeries, including laparoscopic Roux-en-Y gastric bypass, sleeve gastrectomy, and duodenal switch/biliopancreatic diversion procedures.

THESE PROCEDURES ARE RECOMMENDED FOR PATIENTS WITH A BODY MASS INDEX (BMI) OF:

- **30.0–34.9 kg/m²** (Class I obesity) and T2DM with inadequate glycemic control, despite an optimal lifestyle and medical therapy.
- **35.0–39.9 kg/m²** (Class II obesity) and at least one severe obesity-related comorbidity.
- **≥40.0 kg/m²** (Class III obesity), with or without coexisting comorbidities.

Oral Medications and Subcutaneous Injections With Glucagon-like Peptide-1 Receptor Agonists

Commonly known as GLP-1 RAs, these are a class of medications including exenatide, dulaglutide, liraglutide, semaglutide, and tirzepatide.

THESE MEDICATIONS ARE RECOMMENDED FOR PATIENTS WITH:

- **T2DM** and **obesity**.
- A **BMI ≥25 kg/m²**.

Sources: (299-301).

vulnerable to bias because individuals who receive GLP-1 RAs may differ from those who do not in ways that affect cancer risk, such as underlying health status, health care utilization, or lifestyle factors. These differences can make it difficult to determine whether observed reductions in cancer risk are attributable to the medication itself or to characteristics of the people receiving it.

Randomized clinical trials (see **Innovations in Cancer Clinical Trials**, p. 100) remain the gold standard for evaluating treatment effects; however, such trials have not yet been conducted specifically to assess cancer outcomes associated with GLP-1 RA use. In the absence of these data, trial emulation studies provide a valuable approach for approximating the rigor of a clinical trial using real-world data. Accordingly, a recent target trial emulation study among adults with and without T2DM who were overweight or obese found that GLP-1 RA use was associated with a significantly lower risk of endometrial cancer, ovarian cancer, and meningioma, with risk reductions ranging from 25 percent to 47 percent (231).

The use of GLP-1 RAs during and after cancer treatment is an ongoing area of research (see **Improving Quality of Life and Health Outcomes**, p. 155). A recent study found that women with triple-negative breast cancer (TNBC)—a rare and aggressive subtype of breast cancer—who used GLP-1 RAs had significantly lower rates of disease clearance following treatment with chemoimmunotherapeutic agents (302). Notably, a subset of women with TNBC may express GLP-1 receptors that, when activated by GLP-1 RAs, promote chemoresistance and subsequently reduce responsiveness to chemoimmunotherapy. These findings highlight the potential importance of molecular profiling of tumors before initiating GLP-1 RA therapy during cancer treatment among individuals with comorbid conditions, such as T2DM.

The economic burden of weight loss interventions is another important consideration. Although GLP-1 RAs have become increasingly popular for weight management, their benefits generally require sustained long-term treatment. The average 2-year cost of GLP-1 RA therapy was $63,483, compared to $51,794 for bariatric surgery, a difference of nearly $12,000

(303,304). Given the mixed evidence regarding the effects of GLP-1 RA therapies on cancer risk and the slightly greater reduction in obesity-related cancer risk associated with bariatric surgery, future studies should evaluate the long-term comparative effectiveness and cost-effectiveness of these treatment approaches.

A poor diet—high in red and processed meat, and low in calcium, fiber, fresh fruits, and vegetables—is attributable to the development of more than 4 percent of all cancer cases in the United States. Consuming a healthy diet that is balanced in nutritionally dense foods can improve health overall and reduce the risk of cancer (see **Sidebar 16**, p. 66) (305).

Evidence on dietary patterns and cancer risk suggests that associations vary across cancer types and dietary groups. In a large prospective study comparing poultry eaters, pescatarians, vegetarians, and vegans with meat eaters, several dietary patterns were associated with lower risks of specific cancers. Poultry eaters had a lower risk of prostate cancer, while pescatarians had lower risks of colorectal, breast, and kidney cancer. Vegetarians experienced lower risks of pancreatic, breast, prostate, and kidney cancer, as well as multiple myeloma (307).

However, the benefits were not uniform across all cancer sites. Vegetarians had a higher risk of squamous cell carcinoma of the esophagus. Vegans had a higher risk of colorectal cancer compared to meat eaters. Overall, the most robust findings from the study were the lower risk of kidney cancer and the higher risk of esophageal squamous cell carcinoma among vegetarians, highlighting the complexity of the relationship between dietary patterns and cancer risk (307).

Beyond specific dietary patterns, increasing attention has focused on the role of ultra-processed foods (UPFs) in cancer development. UPFs are defined as industrial formulations manufactured from processed substances (e.g., oils, fats, sugars, and proteins) containing little to no whole food, that is, foods that have not been processed (309). A recent study found that individuals with the highest consumption of UPFs had a 41 percent greater risk of lung cancer than those with the lowest consumption (310).

Compared to non-vegetarians, **vegetarians had significantly lower risks of several cancers**, including:

Colorectal	▼**21%**
Stomach	▼**45%**
Leukemia or lymphoma	▼**25%**

Source: (308).

W27

Consuming 20 grams daily of cruciferous vegetables like broccoli, cauliflower, kale, cabbage, and brussels sprouts was associated with an **18% reduction in the risk of developing colorectal cancer in North America and a 23% reduction in Asia**.

Source: (311).

W28

Improving access to healthy foods is an important strategy for reducing cancer risk and promoting overall health. One approach is to eliminate food deserts—areas with limited access to grocery stores and other sources of nutritious foods. However, a recent study found little change in the prevalence of food deserts between 2003 and 2023, declining only from 6.1 percent to 5.5 percent. In contrast, the prevalence of food swamps—areas dominated by restaurants and fast-food outlets—increased substantially during the same period, from 80.2 percent to 88.5 percent (312). These findings suggest that unhealthy food environments remain widespread despite efforts to improve access to nutritious foods.

Additional strategies are needed to encourage healthier dietary choices. Public education campaigns that communicate the role of nutrition in preventing cancer and other chronic diseases could mirror the success of tobacco control initiatives. At the policy level, shifting agricultural subsidies away from commodity crops used in the production of added sugars and highly processed foods and toward fruits, vegetables, and other minimally processed foods could help create a healthier food supply and reduce the burden of cancer and other chronic diseases.

Engaging in regular physical activity at the levels recommended by the Centers for Disease Control and Prevention (CDC) can reduce the risk of nine different types of cancer, with research suggesting that more than 46,000 US cancer cases each year could potentially be prevented if all adults met recommended physical activity guidelines (see **Sidebar 17**, p. 67) (313,314).

In the United States, only 24.3 percent of adults meet the recommended guidelines for both aerobic and muscle-strengthening physical activity (253). However, physical inactivity is not solely a US public health concern; it is a global challenge, with an estimated 31 percent of adults worldwide failing to achieve recommended activity levels (315). An international analysis found that the prevalence of meeting physical activity guidelines declines as country

SIDEBAR 16

Dietary Guidelines for Americans

In January 2025, as part of the "Make America Healthy Again" initiative, the US Department of Health and Human Services and the US Department of Agriculture released the *Dietary Guidelines for Americans, 2025–2030*. This is the most significant reset of federal nutrition policy in decades and urges Americans to consume natural, unprocessed, or minimally refined foods that retain their natural nutrients and fiber.

Special considerations and dietary modifications may be necessary to meet the nutrient needs of specific populations, including children, adolescents, young adults, pregnant and lactating women, older adults, individuals with chronic diseases, and vegetarians and vegans.

The *Dietary Guidelines for Americans, 2025–2030* recommends:

PRIORITIZE PROTEIN AT EVERY MEAL

Consume high-quality, nutrient-dense protein from animal and plant-sourced protein-rich foods. Use healthier cooking methods such as baking, broiling, roasting, stir-frying, or grilling instead of deep-frying. Consume 1.2–1.6 grams of protein per kilogram of body weight, daily.

OPT FOR FULL-FAT DAIRY

Consume 3 servings of full-fat dairy with no added sugars.

EAT VEGETABLES AND FRUITS THROUGHOUT THE DAY

Consume at least 3 servings of vegetables and 2 servings of fruits daily, choosing a variety of colorful, nutrient-dense options.

INCORPORATE HEALTHY FATS

Consume healthy fats such as meats, poultry, eggs, omega-3–rich seafood, nuts, seeds, full-fat dairy, olives, and avocados, ensuring that saturated fats do not exceed 10 percent of daily fat consumption.

FOCUS ON WHOLE GRAINS

Prioritize 2–4 servings of fiber-rich whole grains daily.

Eat the right amount for you

Consume the calories needed based on age, sex, height, weight, and level of physical activity. Hydration is also important and individuals should choose water (still or sparkling) and unsweetened beverages.

Limit the consumption of highly processed foods, added sugars, and refined carbohydrates

Limit intake of ultra-processed foods and avoid sugar-sweetened beverages. No amount of added sugars or non-nutritive sweeteners is recommended as part of a healthy, nutritious diet.

Source: (306).

income increases, with adults living in high-income countries being 26.1 percentage points less likely to meet recommended activity levels than those living in low-income countries. Further, significant differences in physical activity levels based on income and socioeconomic status, both within countries and across countries, were observed, suggesting that many people face barriers to being physically active because of where they live or their access to resources (316). As physical inactivity continues to rise globally, increasing opportunities for regular physical activity could play an

SIDEBAR 17

Physical Activity Guidelines

Incorporation of regular physical activity into daily life is one of the most important things people can do 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)**	**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.	60 minutes per day	150–300 minutes moderate intensity per week or 75–150 minutes vigorous intensity per week	
	Strength Training		
	3 days per week	2+ days per week	3 days per week

Everyone should perform **both aerobic and strength training exercises**; some activities like circuit training, aerobics, and running combine these types of training.

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
- Pickleball

VIGOROUS INTENSITY

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

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

Strength Training

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

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

important role in reducing the burden of cancer and other chronic diseases.

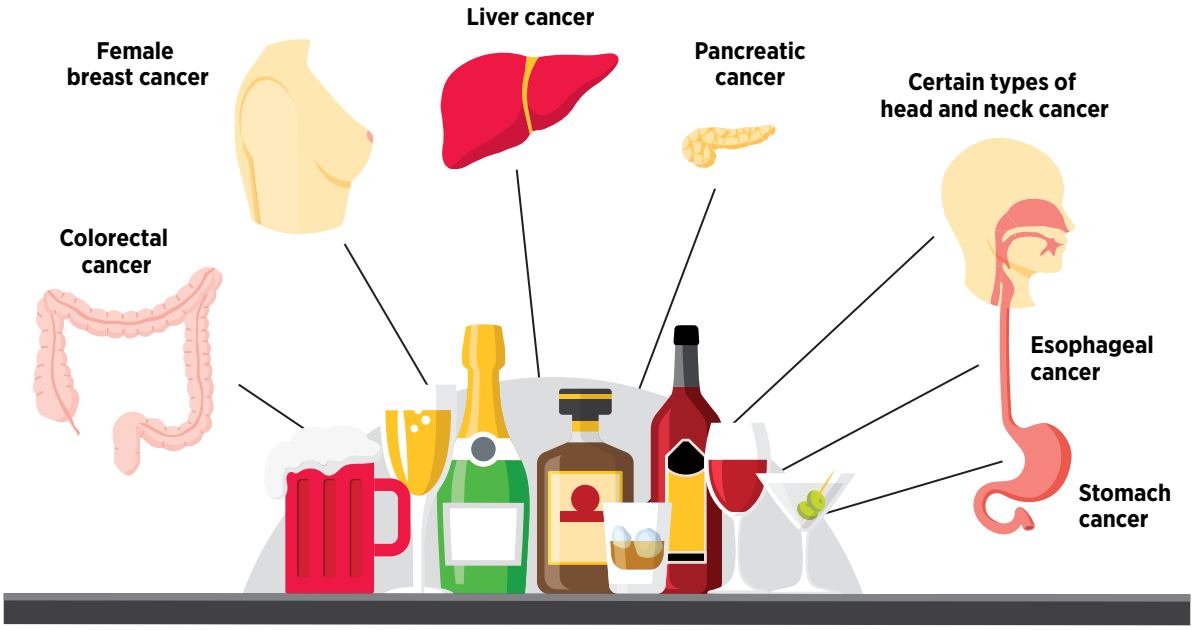
Developing widespread public health campaigns to increase physical activity is essential to reversing the growing trend of sedentary lifestyles in the United States. One example is the Active People, Healthy Nation initiative, which aims to help 27 million Americans become more physically active by 2027. This program focuses on creating activity-friendly communities, promoting physical activity in schools, and partnering with local leaders to implement tailored, community-based programs. On a global scale, WHO's Global Action Plan on Physical

A recent study found that people who regularly achieved the equivalent of about **30 to 45 minutes of brisk walking per day** had a **17% lower risk of developing digestive system cancers** and **13% reduction in digestive-system–specific cancer mortality**.

Source: (317).

W29

FIGURE 11
Alcohol and Cancer Risk



Consumption of any amount of alcohol increases an individual's risk of developing at least seven types of cancer—lip, oral cavity, throat, breast, colorectal, liver, and esophageal squamous cell carcinoma.

Heavy drinking—defined as ≥3 drinks on any day or ≥7 drinks per week for women and ≥4 drinks on any day or ≥14 drinks per week for men—increases the risk of stomach and pancreatic cancers.

Sources: (325,326).

Activity aims to achieve a 15 percent relative reduction in physical inactivity by 2030. The plan outlines a comprehensive framework for creating active societies, active environments, active people, and active systems.

Collectively, national and global efforts recognize that increasing physical activity requires more than individual behavior change; it also depends on creating communities and environments that make active lifestyles safe, accessible, and convenient for all.

Reduce Alcohol Consumption

Alcohol consumption increases the risk for at least seven different types of cancer (see **Figure 11**, p. 68) and is linked to more than 200 diseases (318-323). In the United States, about 5 percent of cancer cases were attributed to alcohol consumption in 2019, the most recent year for which data are available (221,324). This translates to about 97,000 cancer cases and 20,000 deaths.

In 2024, 21.7 percent of US adults age 18 and older—approximately 57 million people—reported binge drinking during the past month (327). While heavy alcohol consumption is a well-established cancer risk factor, alcohol-related cancer risk is not limited to binge or heavy drinkers. Any level of alcohol consumption increases the risk of cancers of the head and neck, esophagus, breast, and colorectum (322,328,329). Higher levels of consumption are associated with increased risk of additional cancers, including cancers of the stomach, liver, gallbladder, and pancreas, although further evidence is needed to establish definitive causal relationships for some sites (330-332).

Despite the established evidence linking alcohol consumption to cancer, public awareness remains limited. A 2026 survey conducted following updates to the US Department of Agriculture Dietary Guidelines—which removed language explicitly stating that alcohol consumption increases cancer risk—found that 53 percent of respondents reported that regular alcohol consumption increases the likelihood of developing cancer, statistically unchanged from 56 percent in February 2025. Sixteen percent reported that alcohol consumption has no effect on cancer risk,

SIDEBAR 18

Guidelines for Alcohol Consumption

The US Department of Agriculture and US Department of Health and Human Services, in the *Dietary Guidelines for Americans, 2025–2030*, advise that people consume less alcohol for better overall health. There are also some people who should not drink at all, such as those who are pregnant or might be pregnant; those under the legal age for drinking; those who have certain medical conditions or are taking certain medications that can interact with alcohol; and those who are recovering from an alcohol use disorder.

If adults age 21 and older choose to drink alcoholic beverages, **drinking less is better for health than drinking more**.

Previous guidelines recommend no more than the following (337):

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.

In 2025, the US Surgeon General issued an Advisory on alcohol and cancer risk. The Advisory provided an overview of the cancers known to be associated with increased risk with alcohol consumption. The Surgeon General also recommends that the label statement on alcoholic beverages needs to be updated to include the following: "There is a direct link between alcohol and fatal cancers," noting that the current label has not been updated since 1988.

while 29 percent were unsure how alcohol affects cancer risk; neither estimate changed significantly from February 2025 (333).

Research suggests that awareness can be improved through targeted education. In a nationally representative study, 70 percent of current drinkers who were previously unaware of the alcohol–cancer connection reported increased awareness after receiving brief educational messages about alcohol and cancer (334). Awareness also varies by beverage type. In a survey examining perceptions of different alcoholic beverages, fewer US adults recognized that wine increases cancer risk (20.3 percent) compared to beer (24.9 percent) or liquor (31.2 percent) (335).

The persistent gap between scientific evidence and public understanding underscores the need for national interventions to raise awareness of alcohol-related cancer risk. Communication strategies, including enhanced warning labels (see **Sidebar 18**, p. 69) and public health messaging, have shown promise in increasing knowledge and influencing drinking intentions. For example, a nationally representative study of 1,036 US adults who consume alcohol found that warning messages addressing specific health outcomes, including colorectal cancer and dementia, were perceived as effective in encouraging reduced alcohol consumption, reminding participants of alcohol-related harms, and providing new information (336).

Between 2008 and 2019, an **estimated 18,463 of the 297,790 new breast cancer cases** diagnosed in the United States are **attributable to alcohol consumption**, including 4,958 cases associated with low levels of alcohol intake.

Source: (329). W30

In July 2025, WHO launched the 3 by 35 Initiative, a global effort encouraging countries to increase the real prices of tobacco, alcohol, and sugar-sweetened beverages by at least 50 percent by 2035 through excise taxes. The initiative aims to reduce consumption of products that contribute substantially to noncommunicable diseases, including cancer, while generating revenue for public health investments. WHO estimates that the initiative could raise an additional $1 trillion (US dollars) in public revenue globally over the next decade and prevent millions of premature deaths, highlighting the potential of coordinated policy approaches to reduce alcohol-related harms worldwide (338).

These findings suggest that strengthening alcohol warning labels and other public education efforts may be an effective population-level approach to reducing alcohol-related harms.

Protect Skin From UV Exposure

UV radiation is a form of invisible energy emitted by the sun. UV radiation is also produced by artificial sources, including tanning beds and sunlamps. Three types of UV radiation exist: UVA, which is largely associated with premature skin aging and wrinkles; UVB, which is the primary cause of sunburn; and UVC, which is generally blocked by the earth's atmosphere and rarely reaches the ground. Exposure to UV radiation, whether from natural or artificial sources, can cause skin cancer, including basal cell carcinoma, squamous cell carcinoma, and melanoma—the deadliest form of skin cancer. In 2026, an estimated 112,000 new cases of melanoma of the skin and 8,510 melanoma deaths are expected in the United States (see **Table 1**, p. 19).

UV radiation is responsible for an estimated 92 percent of melanoma cases and 4.6 percent of all cancers in the United States (221). UV exposure can damage DNA within skin cells, and repeated or excessive exposure can contribute to the development of cancer over time. Although anyone can develop skin cancer, risk is elevated among people with lighter skin tones and those who burn easily. Recent analyses of nationally representative health data found that individuals reporting a history of severe sunburn resulting in blistering or peeling had nearly four- to five-fold greater odds of developing melanoma than those without such a history (339).

Misconceptions about UV exposure remain common. For example, many people believe they are protected from sunburn on cloudy days; however, as much as 80 percent of UV radiation can penetrate cloud cover. Consequently, sun-protective behaviors—including seeking shade, wearing protective clothing, and using sunscreen—are recommended whenever individuals spend time outdoors, regardless of cloud conditions (see **Sidebar 19**, p. 70).

SIDEBAR 19
Ways to Protect Your Skin

To reduce the risk of three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—CDC 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 and can be identified with the label Ultraviolet Protection Factor.

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. Use a 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. Re-apply sunscreen when out in the sun for more than 2 hours and after swimming, sweating, or toweling off.

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

Indoor tanning exposes individuals to the same harmful UV radiation found in sunlight, but in an artificial setting, and increases the risk of skin cancer. WHO classifies tanning beds as a Group 1 human carcinogen, placing them in the same category as asbestos and tobacco smoke. Despite these risks, indoor tanning remains common in the United States, particularly among women ages 18 to 34 years, who have the highest rates of use (340). Evidence indicates that indoor tanning substantially increases skin cancer risk; a recent study found that individuals who used tanning beds had nearly a three-fold higher risk of developing melanoma compared to those who had never used them (341).

In addition to behavioral and public education strategies, advances in sunscreen technology may further strengthen skin cancer prevention efforts. In June 2026, FDA added bemotrizinol to the list of permitted sunscreen active ingredients, making it the first new active ingredient added to the over-the-counter sunscreen monograph since the late 1990s. Bemotrizinol provides broad-spectrum protection against both UVA and UVB radiation and has demonstrated low absorption through the skin into the body. For individuals with darker skin tones, bemotrizinol leaves no white cast and feels lighter and less greasy than other skin protectants currently available (342). FDA determined that bemotrizinol is generally recognized as safe and effective for use in sunscreens by adults and children 6 months of age and older. The addition of bemotrizinol expands the range of sunscreen options available to US consumers and represents an important step toward advancing innovation in skin cancer prevention.

Prevent and Eliminate Infection From Cancer-causing Pathogens

Certain infections caused by viruses, bacteria, and parasites can increase a person's risk of developing cancer (see **Table 2**, p. 72). These cancer-causing pathogens can damage cells, weaken the body's natural defenses, and cause long-term inflammation, all of which can contribute to the development of cancer. In the United States, an estimated 3.4 percent of cancer cases are linked to infections (221). Worldwide, infections are responsible for approximately 10.2 percent of all cancers (343).

Different pathogens contribute to cancer in different ways. Some can directly damage DNA, disrupt normal cell repair processes, produce cancer-promoting substances, or interfere with the mechanisms that control cell growth and division (344). Preventing and eliminating these infections through vaccination, screening, treatment, and other public health measures can play an important role in reducing cancer risk.

Many infection-related cancers can be prevented. Individuals can reduce their risk by taking steps to avoid infection, such as staying up to date on recommended vaccinations, and by seeking treatment to clear infections when appropriate (see **Sidebar 20**, p. 73).

HPV, a group of more than 200 related viruses, is 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 HPV infections do not cause cancer, infection with high-risk strains of HPV for long periods (i.e., persistent infection) can lead to cancer. There are at least 15 high-risk HPV types, of which HPV 16 and 18 are responsible for most HPV-related cancers (349). In the United States, these high-risk HPV strains cause 1.2 percent and 2.5 percent of all cancers in men and women, respectively (221). Globally, HPV-related cancers made up about 7.5 percent of all cancers diagnosed in 2022 (350).

Vaccination is the most effective strategy for preventing HPV infection and the cancers it causes. Evidence of its impact is increasingly apparent at the population level. A recent study found that among women ages 20 to 24 years who received the HPV vaccine, no cervical cancer deaths occurred between 2020 and 2024, compared to 23.1 expected deaths, representing a 100 percent reduction in cervical cancer mortality. Furthermore, compared to the 2000–2014 period, mortality rates decreased by 80 percent among women ages 20 to 24 years during 2015–2019 and by 69 percent among women ages 25 to 29 years during 2020–2024 (351).

The HPV vaccine is approved for females and males ages 9 to 45 years, with routine vaccination recommended at ages 11 to 12 years. The vaccine currently used in the United States, Gardasil 9, protects against nine HPV types associated with cancer. To reduce the burden of HPV-related cancers, the national goal is for 80 percent of adolescents to be fully vaccinated against HPV. Most adolescents who begin the vaccine series before age 15 require two doses, whereas those initiating vaccination between ages 15 and 45 are generally recommended to receive three doses.

Despite broad availability of the vaccine, HPV vaccination coverage remains below the national target. In 2024, the most recent year for which data are available, 63 percent of

In Norway, women vaccinated for HPV between ages 12 and 24 would only need cervical cancer screening every 15 to 25 years, resulting in screening 2 to 3 times per lifetime.

Source: (352).

W31

TABLE 2

Cancer Types and Estimated Cancer Cases Caused by Pathogens Globally

Pathogen	Cancer Types Caused by the Pathogen	Cancer Cases
BACTERIA		
Helicobacter pylori (H. pylori)	Stomach cancer and non-Hodgkin lymphoma	850,000
PARASITES		
Clonorchis sinesnsis (C. sinensis) and *Opisthorchis viverrini (O. viverrini)*	Cholangiocarcinoma	3,500
Schistosoma haematobium (S. haematobium)	Bladder cancer	Not available
VIRUSES		
Epstein-Barr virus (EBV)	Hodgkin lymphoma, certain types of non-Hodgkin lymphoma, nasopharyngeal cancer, and rare stomach cancer	156,600
Hepatitis B virus (HBV)	Hepatocellular carcinoma and other cancers	380,000
Hepatitis C virus (HCV)	Hepatocellular carcinoma and other cancers	170,000
Human herpes virus type-8 (HHV-8)	Kaposi sarcoma	42,000
Human immunodeficiency virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	Not available
Human papillomavirus (HPV)	Cancers of the anus, cervix, head and neck, larynx, mouth, oropharynx, penis, vagina, and vulva	730,000
Human T-cell lymphotrophic virus type-1 (HTLV-1)	T-cell leukemia and lymphoma	3,600
Merkel cell polyomavirus (MCV)	Skin cancer	Not available

Sources: (345-348).

US adolescents were up to date with the recommended HPV vaccination schedule. However, 78 percent had received at least one dose, which has been shown to provide protection against persistent HPV infection (353,354). Emerging evidence suggests that a single dose may provide substantial protection, and CDC has indicated support for simplifying HPV vaccination schedules. However, the Advisory Committee on Immunization Practices currently continues to recommend a two-dose series for individuals who start vaccination before age 15 and a three-dose series for those who begin later.

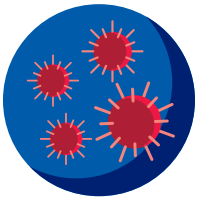
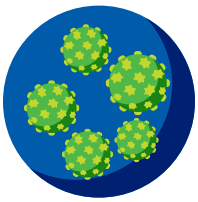
Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can lead to liver cancer and is also a risk factor for other malignancies, including non-Hodgkin lymphoma. Globally, chronic HBV and HCV infection is the most common risk factor for liver cancer and accounts for 55 percent and 21 percent of liver cancer deaths, respectively (347). To eliminate viral hepatitis as a public health threat, the US Department of Health and Human Services (HHS) released the *Viral Hepatitis National Strategic Plan for the United States: A Roadmap to Elimination (2021–2025)* in 2022. The plan outlined goals to prevent new infections, improve health outcomes for those living with viral hepatitis, reduce health disparities, strengthen surveillance systems, and coordinate efforts across sectors to address the hepatitis epidemic.

According to CDC's 2025 *Viral Hepatitis National Progress Report*, the United States met or made progress toward most of its 2025 targets (355). Notable achievements included a 20 percent reduction in new HBV infections, at least a 25 percent reduction in HBV infections among people who inject drugs, a 20 percent reduction in HCV-related deaths, and a 30 percent reduction in HCV-related deaths among Black individuals. Although some targets were not fully achieved—including reductions in HBV-related deaths among Asian or Pacific Islander populations, new HCV infections among people who inject drugs, and HCV-related deaths among American Indian or Alaska Native populations—national trends indicate continued progress toward these goals.

Recent advances in hepatitis B treatment also offer promise for reducing the long-term burden of liver cancer. Current therapies for chronic HBV infection can effectively suppress viral replication but often require lifelong treatment and rarely result in a functional cure. In 2026, FDA granted priority review and breakthrough therapy designation to bepirovirsen, an investigational therapy for chronic HBV infection that

SIDEBAR 20

Ways to Reduce Cancer Risk From Pathogens

Pathogen	Ways to Prevent Infection	Ways to Eliminate or Treat Infection	US Recommendations*
***Helicobacter pylori* (*H. 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 documented history of gastric or duodenal ulcers, low-grade gastric MALT lymphoma, or early stomach 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 with antiviral drugs of those chronically infected 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 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) 	HPV vaccination that protects against 9 HPV types. Practice safe sex, although this may not fully protect against infection.	Subclinical anogenital HPV infection typically clears on its own; therefore treatment is not recommended. Treatment with LEEP is recommended for patients with high-grade cytology (i.e., HSIL) of the anogenital region.	CDC recommends routine HPV vaccination for boys and girls age 11 or 12 (can start at age 9) to young adults age 26 and shared decision-making for catch-up vaccination among adults ages 27 to 45.

HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; MALT, mucosa-associated lymphoid tissue; USPSTF, US Preventive Services Task Force.

* A federal court order paused recent changes to CDC's childhood vaccine recommendations. As a result, the immunization schedule shown here reflects CDC's currently active Child and Adolescent Immunization Schedule by Age at the time of this publication.

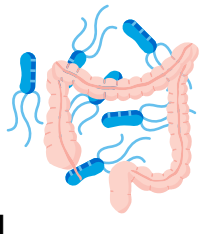
demonstrated clinically meaningful functional cure rates in phase III clinical trials (356,357). Bepirovirsen is designed to reduce HBV proteins and help restore immune control of the infection. If approved, it could become the first therapy capable of achieving functional cure rates substantially higher than those seen with current standard treatments, representing a major advance in efforts to prevent HBV-related liver cancer and other complications.

Helicobacter pylori (*H. pylori*) is a type of bacteria that affects over 40 percent of the global population (358). If left untreated, *H. pylori* infection can lead to stomach cancer. The infection causes chronic inflammation of the stomach lining, which over time increases the risk of developing stomach cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma—a rare form of non-Hodgkin lymphoma.

Epidemiologic studies have consistently shown that chronic *H. pylori* infection increases the risk of non-cardia stomach cancer, and that treatment of the infection reduces that risk (359). Strong evidence also demonstrates that eradication of *H. pylori* lowers the risk of peptic ulcer disease, dyspepsia, and stomach cancer, with a recent study reporting reductions in stomach cancer incidence of up to 44 percent (358).

Because *H. pylori* infection can be identified and treated before cancer develops, screening and eradication have emerged as promising prevention strategies. Although routine population-wide screening for *H. pylori* is not currently recommended in the United States, growing evidence suggests that screening and treatment may be an effective cancer prevention strategy. A recent study found that adding *H. pylori* testing to established colorectal cancer screening programs that use the fecal immunochemical test (FIT) reduced stomach cancer mortality by 13.5 percent and was a cost-effective approach to cancer prevention (361). These findings support ongoing international efforts to expand *H. pylori* screening and treatment as a means of reducing the global burden of stomach cancer.

Emerging evidence suggests that the **effects of *H. pylori* may extend beyond stomach cancer**. *H. pylori*–positive individuals who did not receive antibiotic treatment had a **nearly 3-fold increased risk of colorectal cancer** compared to those who did receive treatment. The increased risk was particularly evident among individuals with positive blood tests for four *H. pylori*–specific antigens (CagA, HpaA, Omp, and HP0305) and those genetically predisposed to developing colorectal cancer.



Source: (360). W32

Limit Exposure to Environmental Risk Factors

Environmental carcinogens are cancer-causing agents that occur in our surroundings and include substances such as arsenic, asbestos, radon, lead, radiation, and a wide range of chemical pollutants. Exposure to elevated levels of these agents, particularly in the absence of adequate protective measures, can increase cancer risk. The International Agency for Research on Cancer (IARC) and the US National Toxicology Program evaluate scientific evidence on environmental exposures and classify known or suspected carcinogens at the international and national levels, respectively. Although these hazards are widespread, exposure is not evenly distributed across populations. Factors such as residential location, occupation, socioeconomic conditions, and daily activities can result in disproportionately high exposure for some individuals.

Air and water are the primary sources of environmental carcinogen exposure. Air pollution results from the release of chemical, physical, and biological contaminants that alter the natural composition of the atmosphere. Common air pollutants include particulate matter (PM), ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide. A growing body of evidence links exposure to air pollution with increased risks of several cancers, including lung (17,139,362-364), breast (365,366), ovarian (367), and, more recently, skin cancer (368).

Emerging research also suggests that air pollution may contribute to cancer development through direct effects on DNA. In a recent study of never-smokers diagnosed with lung cancer, higher exposure to PM was associated with greater levels of DNA damage and specific genetic alterations. Individuals residing in more polluted areas were more likely to harbor mutations in the *TP53* gene, an important tumor suppressor, and to have shorter telomeres, the protective structures at the ends of chromosomes that are often considered markers of cellular aging and damage. A clear dose-response relationship was observed, with increasing air pollution levels associated with greater DNA damage and progressive telomere shortening. Notably, many of the other mutations detected resembled patterns commonly associated with tobacco smoke exposure and aging-related biological processes (139).

In addition to airborne exposures, environmental contaminants in drinking water may also contribute to cancer risk. Potential carcinogens found in water supplies include

SIDEBAR 21

Per- and Polyfluoroalkyl Substances: The Forever Chemicals

Per- and polyfluoroalkyl substances (PFAS) are a class of over 10,000 synthetic chemicals. They resist oil and water, make surfaces slippery or less sticky and temperature resistant, and have been used in manufacturing non-stick cookware, textiles, food wrappers, and firefighting foams since the 1940s. Among these, PFOA and PFOS are the most extensively studied due to their widespread use and persistence in the environment:

Perfluorooctanoic Acid (PFOA)

Surface coatings for stain, oil, and water resistance on household products, carpets, textiles, and food packaging; personal care products; seals; coatings for cables and wires; and construction materials.

Perfluorooctanesulfonic Acid (PFOS)

Imaging devices, semiconductors, dyes, and ink, and in photolithography and electroplating processes. PFOS has been used extensively in firefighting foams.

PREVALENCE OF PFAS:

PFAS are extremely persistent in the environment, it can take hundreds of years for them to degrade, and they have been detected in the blood of over 95 percent of Americans.

WHO IS AT RISK:

Populations at risk for greater exposure to PFAS include individuals who work in facilities that utilize PFAS in production; firefighters; communities with contaminated water that stems from PFAS-releasing sites like industrial sites, military installations, airports, and wastewater treatment plants.

PFAS AND CANCER RISK:

In 2023 the International Agency for Research on Cancer (IARC) designated PFOA as carcinogenic to humans, stating that there is sufficient evidence for cancer in experimental animal models and strong mechanistic evidence that PFOA exhibits key characteristics of carcinogens in humans. Specifically, exposure to PFOA may lead to epigenetic alterations, cell stress from toxic byproducts, and immunosuppressive effects.

While the production of certain PFAS has declined since 2000, these substances are likely to have lingering effects due to the length of time it takes for PFAS to break down naturally.

Sources: (374,375).

arsenic, asbestos, radon, agricultural chemicals, industrial waste products (369,370), and PFAS. PFAS belong to a broader class of endocrine-disrupting chemicals that can interfere with hormonal signaling and other biological pathways involved in cancer development. Growing evidence suggests that exposure to PFAS may be associated with increased risks of several cancers, including thyroid, ovarian, and breast cancers (371-373) (see **Sidebar 21**, p. 75).

In addition to established environmental carcinogens, growing attention has focused on emerging contaminants whose potential health effects are not yet fully understood. More recently, concerns have emerged regarding the widespread presence of microplastics (MPs) and nanoplastics in the environment and their potential role in carcinogenesis, although research in this area is still evolving (376,377).

MPs are tiny plastic particles that are increasingly detected in air, water, food, and human tissues and may pose risks to human health (378). Several mechanisms have been proposed through which MPs could contribute to carcinogenesis, including the induction of chronic inflammation, oxidative stress, DNA damage, and the transport of other environmental contaminants into the body. Two recent reviews identified evidence suggesting a possible link between microplastic exposure and cancer development (379,380). However,

experts caution that the current evidence is insufficient to draw definitive conclusions because most studies have been conducted in cells grown in laboratories or animal models and have examined relatively short-term exposures rather than long-term effects in humans (377). As a result, additional epidemiologic and mechanistic research is needed to better understand the extent of human exposure to MPs and their potential role in cancer development.

Although the health effects of some environmental contaminants, such as MPs, remain under investigation, other environmental exposures have been firmly established as cancer risk factors. Indoor air pollutants, in particular, represent an important source of exposure. One of the most significant is radon, a naturally occurring radioactive gas produced by the breakdown of uranium in soil, rock, and water. Radon can enter buildings through cracks in foundations, walls, and floors, as well as through gaps around pipes, wires, and other openings. Indoor radon concentrations vary geographically and tend to be highest in areas with uranium-rich geological formations.

Exposure to elevated levels of radon is common in the United States. Approximately 83.8 million people live in homes where radon concentrations exceed 148 Bq/m^3, the level at which the US Environmental Protection Agency (EPA) recommends mitigation efforts (381). Analyses of community-level data from 2001 to 2021 identified particularly high concentrations in eastern Pennsylvania, central Ohio, and a large geographic corridor stretching from the eastern Dakotas through western Iowa and eastern Nebraska. In addition, many adjacent areas had radon concentrations approaching the EPA action level, ranging from 111 to 148 Bq/m^3 (381).

Concerns about environmental carcinogens have also expanded beyond air and water pollution to include chemicals found in consumer products. In recent years, studies have linked exposure to certain ingredients in hair care and cosmetic products—including some chemical hair straighteners, relaxers, and synthetic hair products—to increased risks of hormone-related cancers and other adverse health outcomes (232,233). Black women may be disproportionately affected because use of these products often begins in adolescence—a critical exposure window for hormone-related cancers—and continues throughout adulthood, resulting in higher cumulative exposures (384). Growing concern over these findings has prompted legislative action. In 2025, members of Congress introduced the Safer Beauty Bill Package, a series of bills aimed at restricting or banning hazardous chemicals in personal care products, improving ingredient transparency, and strengthening protections for women of color and salon workers who may face elevated exposures (234). These efforts reflect increasing recognition of the potential role of everyday consumer products as sources of carcinogenic and endocrine-disrupting chemical exposures.

Despite the growing concerns that **hair products used by Black women, including hair relaxers and synthetic hair extensions, contain cancer-causing agents** including lead, arsenic, and cadmium, the market for these products was valued at $2.79 billion in 2023 and is projected to exceed $6.34 billion by 2029.

Sources: (382,383). W33

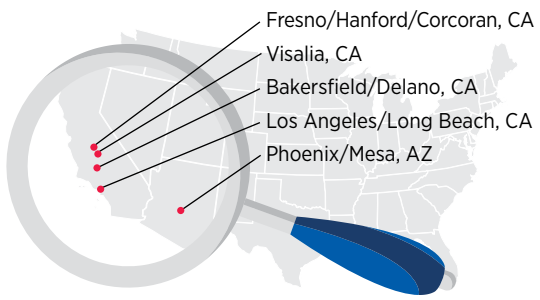
Where You Live Matters

Where an individual lives can have a significant impact on their health and cancer risk. Geographic differences in environmental exposures—including those related to industrial pollution and climate change—can influence the likelihood of developing cancer (226,385-387). Individuals living near industrial facilities may experience greater exposure to toxic chemicals and metals, while those in areas affected by extreme heat, air pollution, drought, or wildfires may face additional climate-related carcinogenic exposures. For example, wildfire smoke can contain cancer-causing chemicals released from burning vegetation, buildings, and other materials (227).

Air pollution is one important example of how geographic location can influence health risks. In 2026, an estimated 152.2 million people lived in areas with unhealthy levels of ozone, a harmful air pollutant formed when emissions from vehicles, factories, and other sources react in sunlight. Additionally, 33.5 million children lived in counties that received an F grade for at least one measure of air pollution, indicating that unhealthy air quality occurred frequently enough to pose potential health risks. Air quality trends also vary substantially across the country. In seven states—Arizona, Connecticut, Louisiana, New Jersey, New Mexico, Oklahoma, and Texas—more counties experienced worsening ozone pollution than showed improvement or no change from 2025 (388).

The effects of climate change, defined as long-term shifts in temperature and weather patterns driven largely by human activity, are an increasing concern among public health experts (227,228). Strong scientific evidence confirms that climate change is occurring and suggests that it intensifies exposure to carcinogens through air, water, occupational, and other environmental pathways. Climate change is increasingly recognized as a determinant of cancer risk and outcomes because it alters the frequency, intensity, and behavior of extreme weather events; modifies environmental exposures; and can disrupt cancer prevention, screening, diagnosis, and treatment services.

Top 5 US Metropolitan Areas Polluted by Ozone



Source: (388).

W34

Climate change can increase exposure to harmful air pollution in several ways. Higher temperatures can worsen air quality, and hotter, drier conditions can increase the likelihood of wildfires. In recent years, climate change has contributed to more frequent, severe, and longer-lasting wildfires in many parts of the United States (389). As these fires spread, they burn not only trees and vegetation but also homes, vehicles, and other human-made materials. This burning releases a mixture of toxic pollutants into the air, including chemicals known or suspected to cause cancer, such as benzene, dioxins, and polycyclic aromatic hydrocarbons (PAHs). People living near wildfire-prone areas may be exposed to these pollutants through the smoke and ash generated by the fires. Although researchers are still working to fully understand the long-term health effects of these exposures, climate-driven wildfires represent a growing source of cancer-related environmental risks (227).

Climate change is expected to further increase geographic disparities in air pollution exposure. Rising temperatures and more frequent wildfires increase the release of ozone-forming pollutants, while hotter conditions and lower wind speeds can allow pollutants to accumulate near the ground. As a result, communities already burdened by poor air quality may experience even greater exposure to pollutants that can adversely affect health and potentially raise cancer risk over time (227,388).

While air pollution is one important pathway through which environmental exposures can influence cancer risk, water quality is another critical concern. Access to clean drinking water varies across communities, and geographic location can affect exposure to a range of cancer-related contaminants (390). For example, a recent study found that public water systems serving communities with higher proportions of residents from households with limited English proficiency were more likely to have detectable levels and higher concentrations of the carcinogens arsenic, chromium, and selenium (391).

Environmental exposures are not distributed equally across the US population. Differences in air quality, water quality, industrial pollution, and climate-related hazards can lead to unequal cancer risks across communities. Understanding and addressing these geographic disparities is critical for reducing the cancer burden and ensuring that all individuals have the opportunity to live in healthy environments.

Occupation Matters

Because of elevated exposure to carcinogens, certain occupations—such as firefighting, industrial painting, and jobs in environments like iron and steel foundries or around welding fumes—have been classified by IARC as Group 1 carcinogens, indicating they are known to cause cancer in humans (392). To reduce risk, workers should consistently use personal protective equipment (PPE) and ensure it is properly decontaminated after exposure to carcinogens and other hazardous substances.

Occupational cancer risk is reflected in differences in cancer mortality across professions. A recent study found that cancer death rates varied substantially by occupation, with some of the highest rates observed among fishing and hunting workers, mining machine operators, and funeral directors (393). Several occupational factors may contribute to these disparities, including differences in access to employer-sponsored health insurance, paid leave, flexible work schedules, and opportunities to seek preventive care or timely treatment. The study also found that a relatively small number of occupations accounted for a disproportionate share of cancer deaths, suggesting that workplace conditions, occupational exposures, and barriers to health care can have a significant impact on both cancer risk and survival (393).

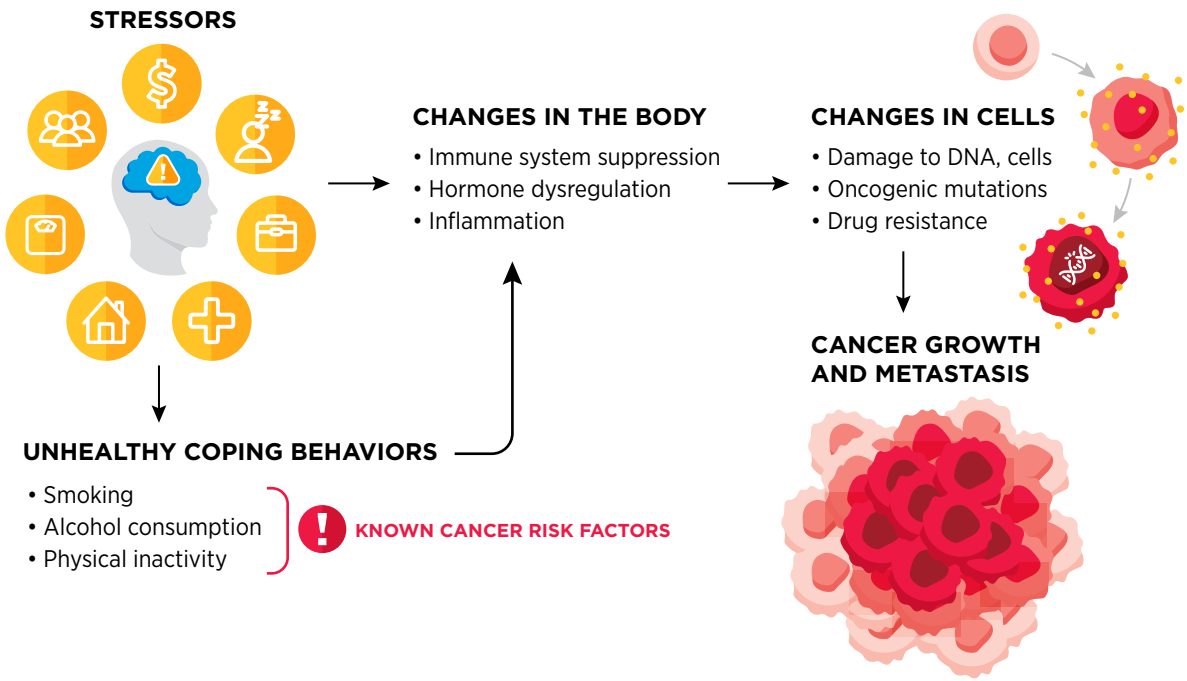
Work schedules may also influence cancer risk. In particular, long-term night shift work has been associated with an increased risk of several cancers (394). Researchers believe this may be due to disruption of the natural circadian rhythm—the internal clock that regulates sleep, hormone production, and other biological processes. Emerging evidence suggests that chronic disruption of these rhythms may promote tumor growth and spread by affecting the body's immune system and other mechanisms involved in cancer development (395).

Manage Chronic Stress

Chronic stress represents a critical pathway through which environmental and social conditions can influence health, including cancer risk and outcomes (see **Figure 12**, p. 78). Rather than reflecting short-term psychological distress,

FIGURE 12

Emerging Role of Stress in Cancer Risk



Stress, or psychological stress, is the body's response to physical, mental, or emotional pressure. Common stressors include everyday responsibilities, such as work, family obligations, and financial concerns. The effects of stress may be influenced by broader environmental and societal factors, including poverty, discrimination, and other adverse social drivers of health. Stress can affect physical and mental well-being in several ways. It can lead to unhealthy coping behaviors, such as smoking, excessive alcohol consumption, physical inactivity, and risky sexual behaviors, all of which are established cancer risk factors. Chronic stress can promote inflammation, disrupt hormone regulation, and impair immune function, all of which play important roles in cancer surveillance and control.

Documenting a causal link between stress and cancer development is an active area of research. Although stress is an unavoidable part of everyday life, helping individuals develop healthier coping strategies may, in turn, reduce their risk of cancer.

Sources: (34,397-403).

chronic stress involves the sustained activation of physiological stress responses due to ongoing exposure to challenging life circumstances. These exposures may include factors such as economic strain, neighborhood conditions, and experiences of interpersonal or structural stress. Conceptual frameworks such as the minority stress model help explain how persistent stressors—such as discrimination or stigma—can affect biological processes over time through repeated activation of stress and inflammatory responses (396).

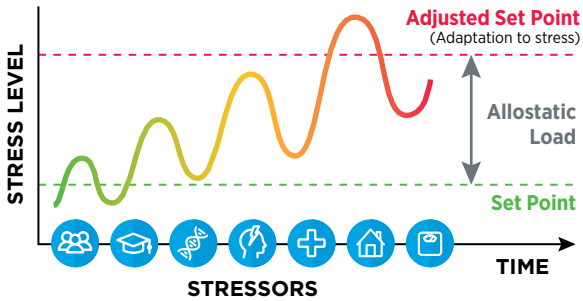
Research has shown that repeated stress over time leads to a pathophysiologic manifestation referred to as allostatic load, which represents the cumulative "wear and tear" on multiple biological systems, including neuroendocrine, immune, metabolic, and cardiovascular pathways (see **Figure 13**, p. 79) (403,404). Elevated allostatic load has been associated with dysregulated immune function and inflammation, which are key mechanisms linking chronic stress to adverse health outcomes such as asthma, diabetes, heart conditions, and cancer (404-411).

Social drivers of health (see **Figure 2**, p. 22), including features of the built environment, are central contributors to chronic stress and allostatic load. Minoritized populations groups and other medically underserved populations are disproportionately exposed to stressors such as economic insecurity, neighborhood disinvestment, residential segregation, environmental hazards,

FIGURE 13

Allostatic Load

What It Is



How It Is Measured

CARDIOVASCULAR RESPONSE
Heart rate (pulse), blood pressure (cuff)

IMMUNE RESPONSE
C-reactive protein (blood), fibrinogen (blood)

METABOLIC RESPONSE
BMI (calculated), waist-hip ratio (measuring tape)

NEUROENDOCRINE RESPONSE
Cortisol (blood, saliva, urine), hormones (blood)

Allostatic load refers to the "wear and tear" on the body that builds up over time when someone is exposed to ongoing stress. When the body is constantly adapting to challenges—like stress, illness, or hardship—the body works to maintain stability through change. Under normal conditions, the body operates around a baseline set point, which is its typical level of physiological functioning, including factors such as stress hormone activity, blood pressure, and metabolism. However, repeated or chronic stress can shift this baseline, causing the body's stress-response systems to adopt a higher adjusted set point. As a result, the body remains in a heightened state of activation even in the absence of immediate stressors. Over time, this cumulative strain can impair organs and systems such as the heart, immune system, and metabolism.

Allostatic load is measured by combining clinical and laboratory biomarkers, including blood pressure, body mass index, lipid levels, glucose metabolism, inflammatory markers, and stress hormones, into an overall score, with higher values indicating greater biological burden. As a biological link between social and environmental exposures and health outcomes, elevated allostatic load is more common among populations exposed to chronic stressors and contributes to disparities in cancer risk, progression, and survivorship.

Sources: (404,407,411,412).

housing instability, food insecurity, over-policing, and limited access to health-promoting resources. These conditions are shaped by historical and contemporary social injustices, and create environments in which stressors are frequent, chronic, and cumulative across the life course. Built environment characteristics—such as exposure to ambient noise, air pollution, overcrowding, unsafe housing, neighborhood violence, lack of green space, and proximity to industrial or high-traffic areas—further amplify physiologic stress responses and contribute to elevated allostatic load.

A growing body of research links chronic stress and elevated allostatic load to cancer risk and outcomes. Chronic stress has been associated with biological processes relevant to cancer development and progression, including immune dysregulation, inflammation, and altered hormonal signaling. Epidemiologic studies have reported associations between psychological stress and several common cancers, including breast, prostate, lung, colorectal, and hematologic cancers (161,193,405,407,413-416). For example, stress-related conditions, including anxiety disorders, have been linked to increased lung cancer risk, and preexisting stress-related diagnoses have been associated with higher cancer mortality, particularly among individuals with advanced-stage or hematologic cancers.

Chronic stress can also influence coping behaviors and engagement with health care. Individuals experiencing sustained stress may be more likely to engage in behaviors associated with increased cancer risk, such as tobacco or alcohol use and poor diet. In addition, cancer diagnosis, treatment, and survivorship can introduce new and ongoing stressors that further increase allostatic load, with downstream effects on physical health, mental well-being, and quality of life for both patients and caregivers. Recent evidence suggests that social factors, including financial strain, social isolation, negative life events, and perceived stress, may heighten stress responses among individuals with cancer (417).

To reduce the physiological impact of chronic stress, engaging in health-promoting activities (e.g., physical activity) can help regulate its biological effects by reducing chronic inflammation. Psychosocial interventions may also play a key role. A recent review found that breast cancer patients who received psychotherapy experienced reductions in emotional distress, intrusive thoughts, and anxiety. Additionally, biomarkers of stress (e.g., cortisol) and the expression of pro-inflammatory and metastasis-related genes were lower and downregulated, respectively, among women who received psychotherapy (402).

Collectively, the evidence highlights chronic stress as a potentially modifiable contributor to cancer risk and outcomes, underscoring the importance of strategies that reduce stress and support overall well-being across the cancer continuum.

Be Cognizant of Hormonal Factors

Lifetime exposure of naturally occurring hormones in the body, as well as hormones used in medications or therapies, can influence an individual's cancer risk. Research has shown that hormonal factors play an important role in the development of several cancers, particularly breast and gynecologic cancers. This section highlights how hormone exposure is shaped by reproductive history, breastfeeding, hormone replacement therapy, and gender-affirming hormone therapy, and how it may contribute to differential cancer risk.

Family Planning, Pregnancy, and Breastfeeding

Reproductive factors that include oral contraceptive use, pregnancy, and breastfeeding influence hormonal exposure and the risk of developing certain types of cancer. For example, oral contraceptives can decrease the risk of ovarian and endometrial cancers but may increase the risk of developing breast and cervical cancers (418,419). A recent literature review found that current or recent hormonal contraceptive use among reproductive age women slightly raises the risk of breast cancer, but the risk returns to the population average within a decade of discontinuation (420). These findings are further supported by a large study of more than two million adolescent girls and premenopausal women reporting that the breast cancer risk varies based on contraceptive formulation (421).

Evidence indicates that the risk of developing certain types of breast cancer increases after recent childbirth (422). However, lifetime breast cancer risk decreases two decades or more after the last pregnancy, and women who have their first pregnancy before age 20 have a 50 percent lower risk of developing breast cancer (423). A recent review of the literature suggests that this transient increase in risk is driven, in part, by a series of biological changes that occur in postpartum breast tissue. These changes resemble wound-healing processes and are characterized by heightened immune activity and tissue remodeling, creating an environment that may promote tumor initiation and growth (424). Further research is needed to understand the unique biology of pregnancy-associated breast cancer, develop screening and prevention strategies for women who are risk, and optimize treatment options to prevent adverse effects on fertility.

Studies have shown that breastfeeding protects against several types of cancer. For example, breastfeeding is associated with reduced risk of breast and ovarian cancers (425). For breast cancer, protective effects of breastfeeding are particularly strong for TNBC, an aggressive subtype that disproportionately affects younger and Black women (426). Evidence indicates that breastfeeding reduces breast cancer risk through several mechanisms, including reduced estrogen exposure, molecular changes in breast tissues, and modulation of the breast microbiome, although additional research is needed to further establish these findings (426).

Hormone Replacement Therapy

Hormone replacement therapy (HRT) aims to relieve the common symptoms of menopause and the long-term biological changes, such as bone density loss, that take place after menopause because of the decline in levels of the hormones, estrogen and progesterone. HRT usually involves treatment with estrogen and progestin or estrogen alone in women who have had all or part of their uterus surgically removed, as they no longer need progesterone, which protects against precancerous changes in the lining of the uterus.

The most comprehensive evidence on HRT and cancer risk comes from the National Institutes of Health (NIH)–funded Women's Health Initiative (WHI), the largest women's health prevention study that focuses on strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in postmenopausal women (427,428). A recent review of WHI studies reveals that estrogen alone is marginally associated with breast cancer risk reduction, while the combined use of estrogen and progestin increases the incidence of invasive breast cancer (427). The review also found that HRT may confer benefit when initiated before age 60 or within 10 years of menopause, while delayed initiation (≥65 years) may increase risks of coronary events and stroke.

Studies have shown that HRT also influences cancer risk in women younger than age 55. In a recent study of nearly half a million women ages 16 to 54, estrogen-only therapy was associated with a reduced risk of breast cancer, while combined estrogen–progestin therapy was associated with an increased

risk of breast cancer diagnosed before age 55, particularly the estrogen receptor–negative and triple-negative subtypes (429). The *5th European Code Against Cancer*, published in 2025, recommends, based on the available evidence, that menopausal women should thoroughly discuss the benefits and risks of HRT with their health care provider and limit its use to the shortest duration possible (430,431).

In the United States, recommendations regarding HRT remain somewhat conflicting. USPSTF recommends against the use of HRT for the primary prevention of chronic conditions in postmenopausal women, regardless of whether they have an intact uterus (432). In contrast, FDA recently revised the labeling of six HRT medications, removing warning language that linked their use to breast cancer and other chronic conditions (433).

An emerging area of research within hormone therapy involves understanding cancer risks associated with gender-affirming hormone therapy (GAHT) (434). In transgender individuals, GAHT uses hormones to help align a person's physical characteristics with their gender identity. For transgender men, testosterone is used to promote masculine features, such as a deeper voice and increased body hair, while reducing feminine characteristics. For transgender women, estrogen is used to promote feminine features, such as breast development and changes in body fat distribution, and medications that lower testosterone levels are often used to reduce masculine characteristics (435).

The available evidence is limited by short follow-up durations and small cohort sizes. A recent systematic review of the literature did not find increased incidence of skin, female breast, or prostate cancers among transgender and gender-diverse individuals receiving GAHT (436). However, evidence from smaller studies indicates that transgender women receiving estrogen therapy have increased risk of advanced-stage prostate cancer; greater duration of estrogen therapy increases their risk of breast cancer (436). Experts emphasize the need for additional research and larger studies to determine cancer risk, so that better, evidence-based prevention and early detection strategies can be implemented for this medically underserved population (436-438).

Cancer Screening for Early Detection

IN THIS SECTION, YOU WILL LEARN:

- Cancer screening refers to checking for cancer, or abnormal cells that may become cancer, in people who do not have symptoms of the disease.
- Routine cancer screening helps save and improve lives by detecting cancer at an early stage when treatment may be curative.
- The United States Preventive Services Task Force, a panel of experts in evidence-based medicine, recommends routine screening for cancers of the breast, cervix, colon and rectum, lung, and prostate.
- Cancer screening uptake among eligible individuals in the United States is suboptimal.
- Disparities in routine screening and follow-up testing have been documented based on race, ethnicity, sexual orientation, gender identity, geography, education, and socioeconomic status.
- Evidence-based interventions are improving access and adherence to routine cancer screening and follow-up care for all eligible individuals.
- Artificial intelligence–assisted approaches, minimally invasive tests for simultaneous detection of multiple cancers, and personalized recommendations based on genomics and other risk factors are exciting new frontiers in cancer screening for early detection.

According to the National Cancer Institute (NCI), cancer screening means checking for cancer, or for abnormal cells that may become cancer, in people who have no symptoms of the disease. Large, population-based studies and randomized clinical trials have shown that routine screening reduces cancer deaths. The key aims of cancer screening are to identify precancerous lesions that can be removed or treated, or to detect cancer at an early stage when treatment is more likely to be less intensive and possibly curative (see **Figure 14**, p. 83) (439).

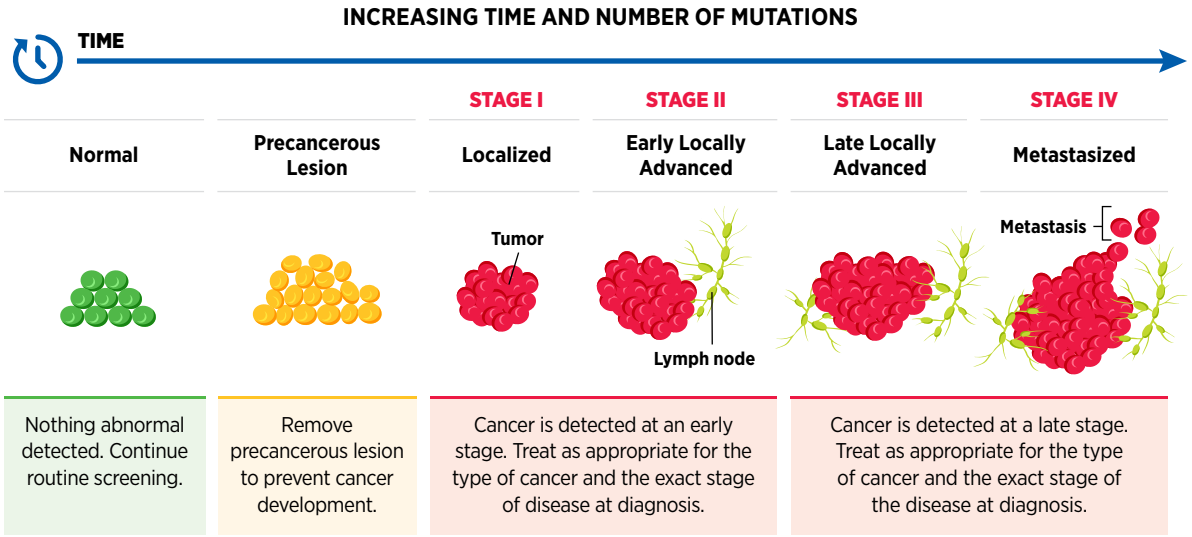
Cancer screening involves several steps, starting with a conversation between individuals and their health care provider about the benefits and risks of screening based on age, biological sex, and personal factors, such as family history. If the screening test shows no concerns, no further action is needed until the next scheduled screening. However, if the test finds possible signs of cancer or unclear results, follow-up care may be needed, including additional testing to confirm a diagnosis and, if necessary, starting treatment (see **Figure 15**, p. 84).

Routine Cancer Screening Saves Lives

Evidence from large, randomized trials and population-based studies has established routine cancer screening as a key to saving lives from cancer. Some of the strongest data have come from colorectal cancer (CRC) screening. One study analyzed data from nine large, randomized clinical trials, covering nearly 830,000 individuals with up to a 10-year follow-up. When comparing no screening to the four United States Preventive Services Task Force (USPSTF)–recommended CRC screening approaches, researchers found that flexible sigmoidoscopy reduced CRC deaths by 26 percent, while guaiac fecal occult blood test reduced CRC deaths by 13 percent (440). The benefit of flexible sigmoidoscopy screening in reducing CRC mortality is reinforced by a 23-year follow-up of nearly 99,000 individuals in a Norwegian randomized trial. Findings from the trial show that the relative risk of death from CRC is reduced by more than a third among screened men, though the benefit was weaker in women (441).

FIGURE 14

What Cancer Screening Can Find and What Can Be Done

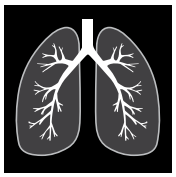


Screening is a regular interval-based assessment that reduces mortality from cancer. Results of cancer screening tests can be negative, positive, indeterminate, or incomplete. If the test does not indicate an abnormality, routine cancer screening should be continued if its benefits for the person continue 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 early-stage cancer, the patient can be treated successfully and has a higher likelihood of better outcomes. If the test finds late-stage cancer, the likelihood of a better outcome may decrease significantly. 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.

Individuals with a family or personal history suggestive of inherited cancer syndromes are considered at higher risk of developing cancer and should discuss genetic counseling and testing with their health care provider.

A key purpose of routine cancer screening is to find cancer or precancerous lesions at the earliest stage when the treatment can be curative (see **Figure 14**, p. 83). One of the ways researchers assess the impact of routine screening is by examining the incidence of early-stage cancers at the population level: An increase in early-stage cancer diagnoses following issuance of screening guidelines indicates that screening is reaching the target population and is detecting cancers at an earlier, more treatable stage. For example, the 2021 USPSTF recommendation lowering the CRC screening start age to 45 increased screening uptake in adults ages 45 to 49 from about 20 percent to 34 percent between 2019 and 2023 (443). Furthermore, early-stage CRC diagnoses in this age group also increased 50 percent between 2021 and 2022 (444), indicating that the revised screening guidelines are finding CRC earlier in this age group, reducing the likelihood of advanced-stage diagnosis and CRC-related mortality.

In 2024, **lung cancer screening uptake** in the United States was 19%; **a modeling study projected that increasing it to 100%** would have led to:



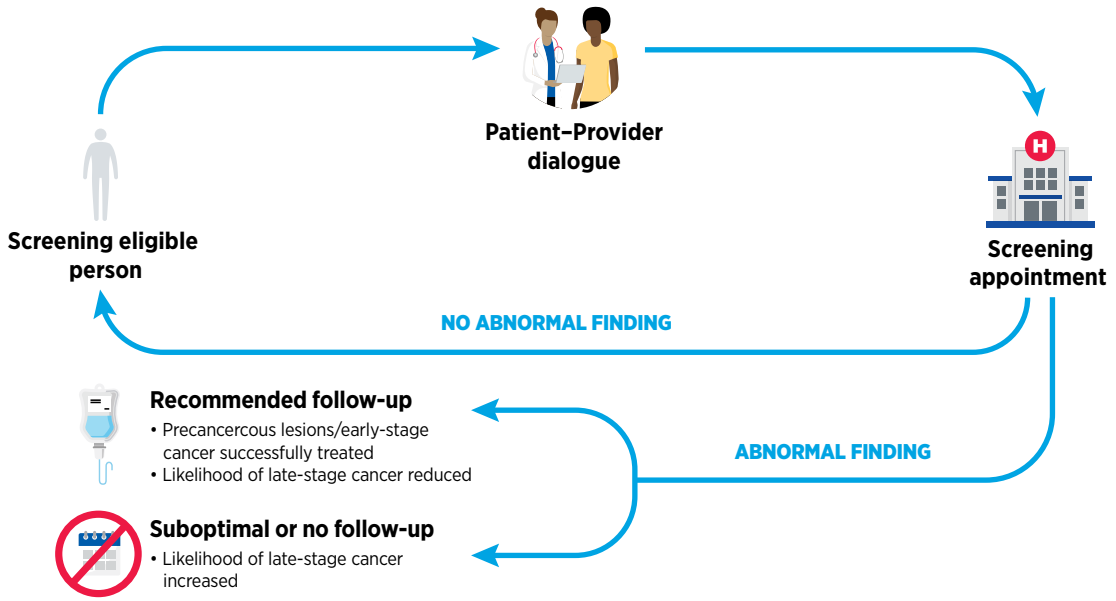
47,140
additional deaths prevented*

682,240
life-years gained*

* Over 5 years.
Source: (442).

W35

FIGURE 15
Cancer Screening Continuum



Screening for cancer is a continuum that involves multiple steps, starting with a dialogue with a health care provider, receiving the routine cancer screening test, and additional follow-up testing and/or treatment if the results of the routine cancer screening test are inconclusive or abnormal and the follow-up testing identifies precancerous lesions or cancer.

The impact of routine screening on reducing cancer mortality accumulates over time as more early-stage cancers and precancerous lesions are found and treated. This means that studies require decades-long follow-up to capture the full impact of routine cancer screening, necessitating the need for sustained and predictable funding for public health research.

Evidence Guides Cancer Screening Recommendations

Panels of subject matter experts, convened by government agencies and professional public health organizations, translate findings from screening trials into population-level guidance for routine cancer screening. The multistep process typically includes a comprehensive review in which experts weigh the evidence for benefits and potential harms of recommending screening, including at what age to start and stop routine screening and which tests to use. This report focuses on the recommendations issued by USPSTF, a congressionally mandated independent panel convened by the US Department of Health and Human Services. USPSTF issues screening recommendations based on individuals' lifetime risk of developing cancer.

People at average risk are those without a significant personal or family history of cancer or a known inherited genetic condition. For these individuals, screening recommendations are generally based on age and biological sex. People exposed to cancer risk factors, such as smoking tobacco or environmental carcinogens, have a higher likelihood of developing cancer (see **Reducing the Risk of Cancer Development**, p. 55). Other groups of individuals with increased risk include those diagnosed with cancer (see **Advancing Cancer Survivorship Care**, p. 144), those with multiple immediate family members diagnosed with cancer, and those with hereditary cancer syndromes. The composition of specific tissues can also influence the risk of developing cancer. For example, women with dense breast tissue have a higher risk of developing breast cancer. Identifying approaches that can supplement routine mammography, such as magnetic resonance imaging (MRI), for detecting breast cancer early in women with dense breasts is an area of active investigation (445,446).

Based on the strength of evidence, USPSTF assigns a letter grade to its recommendations that indicates whether the benefits of routine screening outweigh the potential harm (see **Sidebar 22**, p. 85). Sometimes, USPSTF gives different grades for different groups of people for the same type of

SIDEBAR 22

USPSTF Guidelines for Cancer Screening

Cancer Type	Recommendations*	Grade†
BREAST	Screening mammography is recommended every other year for women ages 40 to 74.	B
	Screening mammography is not recommended for women age 75 or older.	I
CERVICAL	Cervical cytology is recommended every 3 years for women ages 21 to 65; high-risk human papillomavirus testing alone, or in combination with cytology, every 5 years for women ages 30 to 65.	A
	Screening is not recommended in women younger than 21 years or older than 65 years.	D
COLORECTAL	Screening is recommended for all adults ages 50 to 75.	A
	Screening is recommended for all adults ages 45 to 49.	B
	Selective screening in adults ages 76 to 85 through an ongoing dialogue between patient and health care provider that considers patient's overall health, prior screening history, and preferences.	C
LUNG	Annual screening with LDCT is recommended for adults ages 50 to 80 who have a 20 pack-year‡ smoking history and who currently smoke or stopped smoking within the past 15 years. 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.	B
PROSTATE	An individual decision, through ongoing dialogue between patient and a health care provider, whether to receive periodic PSA–based testing; recommended for men ages 55 to 69.	C
	PSA-based screening is not recommended in men age 70 and older.	D

LDCT, low-dose computed tomography; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

* Indicated here are only USPSTF recommendations for individuals at an average risk of developing cancers of the breast, cervix, colon and rectum, and prostate, or those at a high risk of developing cancer of the lung and bronchus. Several other professional societies issue evidence-based screening guidelines for types of cancer listed here that may differ from those issued by USPSTF. Furthermore, guidelines have been simplified for brevity. Readers are advised to visit the USPSTF website for a complete description and more detailed information.

† Grade A: Screening is recommended because of high certainty that net benefit is substantial.
Grade B: Screening is recommended because of high certainty that net benefit is moderate.
Grade C: Selective screening is recommended based on professional assessment and patient preferences because of moderate certainty that net benefit is small.
Grade D: Screening is not recommended because of moderate to high certainty that screening has no net benefit, or that the harm outweighs the benefits.
I Statement: Insufficient evidence to assess the balance of benefits and harms of screening.

‡ A pack-year is a way to measure the amount a person has smoked over a long period. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack-year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year, and so on.

cancer. In some cases, USPSTF recommends against screening if the harm is likely to be greater than the benefits. When evidence is lacking to make a clear recommendation, USPSTF issues an Insufficient Evidence Statement.

The USPSTF grade determines whether a screening test is covered without out-of-pocket costs under the Patient Protection and Affordable Care Act (ACA). Although USPSTF is officially scheduled to meet three times per year, the panel has not met since March 2025, delaying potential revisions to screening guidelines for cervical and prostate cancers (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 189).

In addition to USPSTF, many professional organizations focused on public health also issue screening recommendations through similarly rigorous processes. These screening recommendations are widely used in the clinic, although not all are covered by insurance plans. Because new evidence for better screening approaches is constantly emerging, it is important for screening-eligible individuals to have a continued dialogue with their providers to stay up to date with the latest evidence guiding cancer screening and revise their screening plans accordingly.

Tests for Cancer Screening

Cancer screening tests are medical procedures that detect signs of cancer or precancerous lesions directly (e.g., by imaging the tissue) or indirectly (e.g., by analyzing blood or other biospecimens for cellular or molecular signs of cancer) (see **Sidebar 23**, p. 87). Most screening tests are noninvasive, but some (e.g., colonoscopy) are invasive medical procedures that can in rare cases cause complications, such as bleeding. Like any other medical procedure, screening tests can yield false-positive results, causing unnecessary follow-up testing, concern, and anxiety. Sometimes, screening tests can miss signs of cancer, delaying diagnosis. In some cases, screening tests can detect slow-growing cancers or unrelated medical conditions that would not have caused harm in a person's lifetime; these findings can lead to medical procedures that may not have been necessary.

Because of the potential harms associated with screening tests, USPSTF and other organizations carefully weigh the benefits of tests against any potential risks, with the goal of minimizing overdiagnosis, missed diagnoses, and unnecessary follow-up testing and treatments, while reducing cancer burden at the population level. As new tests are approved by regulatory bodies, organizations revise screening guidelines to incorporate improved screening approaches. In recent years, the US Food and Drug Administration (FDA) approvals of at-home self-collection kits for human papillomavirus (HPV) testing and new blood- and stool-based tests for CRC screening prompted the American Cancer Society to update its screening guidelines for cervical and colorectal cancers and include these tests into its recommendation (447). It is important to note that the CRC guidelines explicitly recommend using blood-based tests only for individuals who decline or have not completed a preferred test. This caution is issued because blood-based tests have lower sensitivity for detecting advanced precancerous lesions and stage I cancer.

The **SHIP Trial** (Self-collection for HPV testing to Improve Cervical Cancer Prevention Trial) is an **NCI-funded multicenter study evaluating whether self-collected vaginal samples for human papillomavirus (HPV) testing are as accurate as clinician-collected cervical samples**.

Based on data from the SHIP Trial, FDA approved the first comprehensive at-home HPV self-collection kit in April 2026.

Source: (448).

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Research Improves the Science of Cancer Screening

An important area of cancer research is understanding how screening guidelines, when implemented at the population level, impact the burden of cancer. Researchers use real-world data to improve screening guidelines; some studies reinforce existing guidelines, while others inform better approaches to screening. For example, findings from a recent study of more than 91,000 US veterans show that colonoscopy screening after age 75 may offer limited benefits, even in individuals who were previously diagnosed with adenoma—non-cancerous growths in the colon (449). Researchers found that adults who reached age 75 with a prior diagnosis of adenoma had a very low 10-year risk of developing CRC or dying from it (1.1 percent and 0.5 percent, respectively). By comparison, nearly half died from unrelated causes within the same period (449). These findings further corroborate the current USPSTF recommendation that CRC screening in adults older than 75 years should only be done through a dialogue between the individual and health care provider that considers individual preferences, overall health status (e.g., life expectancy and comorbidities), and prior screening history (e.g., those who have never been screened are more likely to benefit than those routinely screened until age 75) (see **Sidebar 22**, p. 85).

Evidence is accumulating that precancerous lesions are detected at substantially lower rates in women with a long

SIDEBAR 23

USPSTF-recommended Tests to Screen for Cancer

USPSTF is an independent panel of experts in preventive care who rigorously review evidence on the benefits and harms of screening strategies, behavioral counseling, and preventive medications related to cancer and other diseases. Tests described below are a part of evidence-based cancer screening recommendations by USPSTF.

	USPSTF-recommended Tests*		
Cancer Type	**Name**	**What It Is**	**What It Does**
BREAST	Digital mammography	Imaging test	Uses low-dose X-rays to look for early signs of breast cancer.
	Digital breast tomosynthesis (3D mammography)	Imaging test	Uses low-dose X-rays to generate 3D images of the breast that are analyzed for signs of cancer. Must be accompanied by digital mammography.
CERVICAL	Pap test (Pap smear)	Cytologic test	Looks for abnormal cells in the cervix that may turn into cancer.
	HPV test	Molecular test on cervical sample	Detects HPV types that cause cervical cancer.
COLORECTAL	FIT	Stool test	Uses antibodies to detect a product of red blood cells in stool that can be a sign of colorectal cancer.
	High-sensitivity gFOBT	Stool test	Uses a chemical reaction to detect a product of red blood cells in stool that can be a sign of colorectal cancer.
	Stool DNA-FIT	Stool test	Looks for colorectal cancer–related DNA changes and a product of red blood cells in stool.
	Colonoscopy	Endoscopic imaging test	Uses a camera-tipped tube to check the entire colon for colorectal cancer or polyps.
	Flexible sigmoidoscopy	Endoscopic imaging test	Checks for colorectal cancer or polyps in the lower part of the colon.
	CT colonography (virtual colonoscopy)	Imaging test	Uses X-rays to image the colon and rectum.
LUNG	LDCT	Imaging test	Takes detailed images of the lungs to find cancer early.
PROSTATE	PSA test	Blood test	Measures a protein in blood that can be higher in men with prostate cancer.

3D, three-dimensional; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; HPV, human papillomavirus; LDCT, low-dose computed tomography; Pap, Papanicolaou; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

* For cancer types for which there are more than one USPSTF-recommended test to screen for cancer, the frequency of routine screening varies by the test used to screen for the indicated cancer. Based on an individual's risk of developing cancer, the health care provider may recommend which test to use. A continuing dialogue with the health care provider is important to stay up to date with routine screening recommendations, including which tests may be most beneficial.

history of negative cervical cancer screening, supporting the use of longer intervals between screenings. A recent study of approximately 1.7 million women undergoing HPV and cytology co-testing every 3 years found that cervical cancer diagnosis fell eight-fold by the fifth screening round compared to the first (450). Another recent study of 8,078 women with a follow-up of up to 10 years found that a negative HPV result alone conferred precancer risk similar to a negative co-test, suggesting that adding cytology to primary HPV screening provides limited additional benefit (451). Taken together, these findings support both extending screening intervals and streamlining screening protocols for women with established negative HPV histories.

Screening guidelines can sometimes contribute to disparities. USPSTF eligibility criteria for lung cancer screening, issued in 2021, is partly based on smoking history. Research has shown that Black individuals develop lung cancer at lower levels of tobacco exposure than White individuals, and thus often are not screening-eligible (452). A large study compared the 2021 USPSTF lung cancer screening guidelines with the 2023 American Cancer Society guidelines that removed the requirement for time since smoking cessation. Researchers found that removing smoking history as a criterion increased eligibility across population groups, although the magnitude of screening eligibility was higher for White individuals. Compared to the 2021 USPSTF guidelines, the change also widened disparities in lung cancer screening between White and Black individuals by 5 percentage points and between White and Hispanic individuals by 10 percentage points (453). These findings emphasize how eligibility criteria designed around population averages can exacerbate disparities in routine cancer screening (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 189).

Effective Strategies Increase Screening Uptake

Despite strong evidence showing that routine screening saves lives, receipt of cancer screenings in the United States varies widely across different cancer types and among different segments of the US population (see **Table 3**, p. 89). Screening rates are especially low among medically underserved individuals, including those belonging to racial and ethnic minority populations, residents of sovereign Native Nations, and people with limited access to health care.

In addition to routine cancer screening uptake, considerable gaps also exist along the cancer screening continuum (see **Figure 15**, p. 84). Because of a multitude of structural and socioeconomic barriers, many individuals whose screening test indicates a suspicious finding often do not follow up to confirm or rule out the initial observation (see **Sidebar 24**, p. 90).

Evidence-based strategies, such as patient navigation, have proven effective at increasing screening uptake and follow-up care. In this section, we highlight key evidence-based strategies, with examples from recent studies, that have proven successful in increasing routine screening uptake and ensuring follow-up after abnormal results.

Reducing Structural Barriers

Disparities across the cancer screening continuum are primarily driven by structural and systemic barriers that particularly affect individuals belonging to racial and ethnic minority groups and other medically underserved populations. Research has shown that removing or reducing these barriers can meaningfully improve screening uptake and follow-up diagnostic testing across all population groups in the United States.

Several studies have established that mailing a fecal immunochemical test (FIT) kit directly to screening-eligible individuals is the most effective intervention for increasing CRC screening. In a recent study of more than 20,500 adults ages 45 to 49 years, the rate of completing CRC screening within 6 months was 26.2 percent among individuals who received an FIT kit by mail without needing to opt-in, outperforming individuals who had to actively choose whether to receive FIT-only screening (16.4 percent), colonoscopy-only screening (14.5 percent), or both (17.4 percent) (464).

Safety-net hospitals, often the primary point of care for underserved populations, show some of the starkest disparities in screening. In these low-resource settings, interventions that remove structural barriers have been shown to be highly effective. In a recent study, 1,275 adults with new FIT orders across eight Federally Qualified Health Centers were sent three behaviorally informed automated text reminders—which incorporated a specific return-by date, an indication that the provider is waiting to receive the test, and a message that the test can save their life—on days 2, 5, and 8 after the FIT order. The text-based intervention achieved 59 percent FIT completion within 21 days, compared to 49 percent FIT completion with the standard nurse-led single call on day 8 (465). Importantly, the text-based approach was cost-effective compared to the telephone outreach in reaching individuals from diverse racial and ethnic backgrounds and with different insurance statuses.

Evidence is accruing that direct-to-patient digital tools can extend access to lung cancer screening, which has the lowest uptake among USPSTF-recommended cancer screening tests (see **Table 3**, p. 89). In a recent study of more than 1,300 adults meeting eligibility criteria, researchers at two academic

TABLE 3

Percentage of Eligible Individuals Up to Date With USPSTF Screening Guidelines in the United States

	Cancer Type*	BREAST†		CERVICAL	COLORECTAL	LUNG	PROSTATE
	Age (Years)	50–74	40–74	21–65	45–75	N/A	50+
	Overall	80	73	75	63	19	37
Race and Ethnicity	AIAN only or multiple	74	62	67	57	‡	23
	Asian only	81	76	63	57	‡	26
	Black only	86	80	73	64	19	34
	Hispanic	78	68	68	53	‡	27
	White only	79	72	80	67	19	41
SOGI	Bisexual	‡	64	79	66	N/A	‡
	Gay/Lesbian	80	69	71	73	N/A	54
	Heterosexual	80	73	76	64	N/A	37
Immigration Status	Born in US/US territory	80	73	78	67	N/A	39
	In US 10+ years	81	73	67	56	N/A	30
	In US <10 years	66	60	55	41	N/A	‡
Education	College graduate	85	79	84	71	19	48
	Less than high school	70	64	59	49	16	22
Income Level	<100% FPL	69	61	65	49	21	21
	≥200% FPL	83	76	78	66	18	41
Insurance Status	Medicaid/Public/Dual eligible	72	67	70	59	20	22
	Medicare (≥65 years)	83	83	60	83	26	46
	Private	83	78	79	68	19	38
	Uninsured	50	42	57	24	‡	13
Urbanicity	Metropolitan	81	74	75	64	19	38
	Nonmetropolitan	76	66	73	61	18	33

AIAN, American Indian or Alaska Native; FPL, federal poverty level; N/A, not available; SOGI, sexual orientation and gender identity; USPSTF, US Preventive Services Task Force.

* Data years: breast cancer, 2024; cervical cancer, 2021; colorectal cancer, 2023; lung cancer, 2024; and prostate cancer, 2023.

† Two age ranges are shown to reflect the 2024 USPSTF guidance to start breast cancer screening at age 40. Data included in the ages 40–75 column are presented only as baseline estimates, as this recommendation was not in place at the time the referenced survey was conducted. Estimates are age-adjusted using 3 age groups: 40–49, 50–64, and 65–74 years.

‡ Estimates are statistically unstable and not shown.

All numbers in this table are rounded to the nearest integer.

Source: (36).

health care systems compared the effectiveness of a digital health program that assessed eligibility, reviewed benefits and harms of screening, and allowed patients to directly request a screening appointment with enhanced usual care that involved individuals receiving a notification of their eligibility and advice to discuss screening with their primary care physician. Findings show that the digital health program increased low-dose computed tomography (LDCT) completion across all population groups within 16 weeks, compared to enhanced usual care (24.5 percent vs. 17.0 percent, respectively) (466).

Integrating Patient Navigation

Patient navigation is one of the most effective strategies for reducing disparities across the cancer care continuum, including routine screening (467). Navigation programs address logistical and structural barriers disproportionately affecting underserved populations by providing help with medical appointments, transportation, and insurance questions, among other needs.

SIDEBAR 24

Disparities and Barriers Across the Cancer Screening Continuum

Racial and ethnic minority groups and other medically underserved populations in the United States facing structural and social barriers experience disparities across the cancer screening continuum, including in uptake and follow-up diagnostic tests when the initial cancer screening test shows abnormality. Examples from recent studies presented here highlight some of the disparities and barriers across the cancer screening continuum. Disparities and barriers across the cancer screening continuum are covered in greater depth in the recently released *AACR Cancer Disparities Progress Report 2026*.

Breast Cancer Screening	• **Only 59 percent of US women** ages 40 to 49 **reported biennial mammography**, while 15 percent were overdue and 26 percent had never been screened (454). • Compared to straight women, **bisexual and queer women** were about 9 percent **less likely to be up to date with mammography screening** (455). • Among women ages 50 to 74, **those without a personal health care provider** were 46 percent **less likely to receive guideline-adherent mammography** screening compared to those who had a provider (456).
Cervical Cancer Screening	• **Only about half** of screening-eligible **women with physical disabilities were up to date** with **cervical cancer screening**, with reported barriers including inaccessible exam settings, physical challenges during pelvic exams, and negative clinical interactions (457).
Colorectal Cancer Screening	• **Unmet social needs**, such as housing instability, food insecurity, and transportation barriers, **were associated with lower colorectal cancer screening** rates, particularly among adults ages 50 to 64 (458). • **Fewer than half of patients complete follow-up colonoscopy** within 6 months after an abnormal stool test, with only 37 percent of Black patients and 39 percent of patients with Medicaid coverage receiving timely follow-up in a large multisystem analysis (459).
Lung Cancer Screening	• In a centralized lung screening program, **Asian participants** were 58 percent **less likely to stay up to date with annual lung cancer screening** compared to other racial groups. In addition, individuals with lower educational attainment were 26 percent less likely to adhere to annual screening (460).
Prostate Cancer Screening	• Among 9,723 men, **only 24 percent reported discussing benefits and harms of prostate-specific antigen (PSA) testing with a provider**, while 63 percent had no discussion at all, with markedly lower engagement among men with less education (461). • In a study of **transgender women** age 50 and older, **only 23 percent** had ever **received PSA screening** (462).
Barriers to Screening	• A geographic analysis found that **US counties with persistently low screening** for breast, cervical, and colorectal cancer were consistently **characterized by higher poverty rates, lower household incomes, and lower educational attainment**, compared to counties with persistently high screening (463).

IN AN ANALYSIS OF
76 RANDOMIZED TRIALS ENCOMPASSING MORE THAN 400,000 PARTICIPANTS
PATIENT NAVIGATION INCREASED COLORECTAL CANCER SCREENING
UPTAKE BY 58% COMPARED TO USUAL CARE

Source: (470). W37

A recent analysis of 42 randomized clinical trials with more than 39,000 participants reported that navigation increased breast cancer screening rates by 13.8 percentage points and cervical cancer screening rates by 15.6 percentage points at 1 year. These benefits were consistent across different sociodemographic groups (468). A randomized clinical trial of more than 5,600 Medicaid enrollees across 28 rural clinics in Oregon showed that a combined mailed FIT outreach and patient navigation program increased CRC screening by 7.3 percentage points over usual care. Navigation to colonoscopy after an abnormal FIT result increased the follow-up completion from 15.4 percent to 43.3 percent (469).

Findings of a randomized trial in a safety-net health system setting showed that cervical cancer screening participation increased from 17 percent with telephone reminders alone to 41 percent with mailed self-collection kits and 47 percent when self-collection was combined with patient navigation (471). In addition to being effective in increasing screening uptake, patient navigation is also cost-effective. As one example, a patient navigation program, funded by the Centers for Disease Control and Prevention (CDC), at a large Federally Qualified Health Center increased the FIT return rates from 36.6 percent to 51.0 percent over 3 years, while the cost per person completing FIT screening decreased from $32 to $25 (472).

In 2024, CDC's Community Preventive Services Task Force formally recommended patient navigation to increase cancer screening and advance health equity (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 189).

Engaging Communities

Community engagement brings screening to patients rather than waiting for patients to seek care. Faith-based organizations and other trusted local institutions represent important platforms for community engagement. In one study, researchers developed a community-based program with input from members of Black churches to improve awareness and engagement with lung cancer screening. The program used culturally tailored messaging and trained lay health advisors. Pilot testing of the program showed strong participant satisfaction and increased knowledge about lung cancer screening (473).

Culturally tailored education tools extend community engagement beyond outreach alone, particularly in populations in which health literacy and structural barriers limit routine screening. A recent study involving 167 participants, nearly 70 percent of whom were Hispanic, evaluated a 12-minute bilingual video on breast cancer screening (474). Participants showed significant improvements in breast cancer knowledge and intention to undergo mammography. Long-term follow-up studies will be important to determine whether an increase in knowledge about breast cancer screening leads to increased uptake in routine screening.

A randomized clinical trial of 797 low-income Hispanic women tested whether group education and telephone navigation delivered by community health workers impact cancer screening uptake in this group. Findings showed that the intervention more than doubled cervical cancer screening completion compared to a control group (55.8 percent vs. 27.4 percent, respectively) and nearly doubled mammography completion (39.9 percent vs. 20.3 percent, respectively) (475).

Community engagement is an effective intervention because it addresses multiple barriers simultaneously, such as cultural stigma, logistical challenges, and mistrust of health systems. Such interventions also help normalize screening within broader social networks, which can influence behaviors at the individual and group levels.

Technological Innovations Advance the Science of Cancer Early Detection

Transformative advances in genomics, artificial intelligence (AI), and minimally invasive tests that can simultaneously detect multiple cancers are rapidly changing the landscape of cancer screening for early detection. In this section, we discuss some of the most promising technological innovations that are poised to revolutionize the field in coming years.

Advances in AI-assisted Screening Approaches

The use of AI in cancer screening has increased rapidly, in part because of its potential to bridge existing gaps in the screening continuum, including missed cancers, false-positive findings, and radiologists' workload. For example, current workflows for routine cancer screenings that use imaging rely on image analyses by multiple radiologists, the clinicians who specialize in interpreting radiologic images for diagnosis and treatment

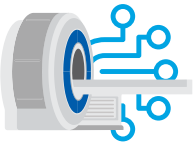
of disease. Studies have shown that the demand for imaging is outpacing the growth in the number of radiologists entering the US workforce and is causing an ongoing and severe shortage (476). This trend is worsened by the finding that the proportion of radiologists leaving the workforce more than doubled from 1.1 percent in 2014 to 2.5 percent in 2022 (477).

Rapid advances in AI-assisted screening tools have emerged partly in response to existing clinical challenges (e.g., missed cancers) and partly to mitigate a critical radiologist shortage. The use of AI-assisted tools in breast cancer screening is a prime example, as reflected by recent findings from major clinical studies. In the first large randomized controlled trial of AI in breast cancer screening, involving more than 105,000 women, AI-supported mammography showed consistently favorable outcomes compared to standard double reading, while also reducing the radiologists' workload (478). AI-supported mammography detected early-stage breast cancer with greater sensitivity than the standard screening yet was just as specific. Importantly, AI-supported screening resulted in 12 percent fewer interval cancers—cancers diagnosed during the time between a regular screening mammogram that appears normal and the next screening mammogram—and 16 percent fewer interval cancers that were invasive. Equally important, prior findings from the study reported a 44 percent decrease in screen reading workload (479).

Findings from another clinical trial of more than 31,000 women demonstrated that an AI-based triage strategy could significantly reduce radiologist workload by safely excluding low-risk mammograms from radiologist readings without a significant difference in cancer detection rate (480). Similarly, a multicenter study of more than 115,000 mammograms found that AI-supported evaluation of images not only was more sensitive but also detected cancer at a higher rate compared to human first readers, while also detecting 25 percent of interval cancers that standard screening missed (481).

Regulatory approvals of AI-assisted cancer screening tools further underscore the emerging role of AI in early detection of cancer. In early 2026, FDA cleared two AI-powered lung cancer screening tools. One of them, RevealAI-Lung, analyzes incidental lung nodules from computed tomography (CT) scans and assigns a score based on the risk of malignancy (483,484). The second, called eyonis LCS, is designed to analyze imaging data generated from LDCT scans and assist radiologists in detecting and characterizing lung nodules, supporting clinical decision-making and patient follow-ups (485).

In a study of 2,686 **patients undergoing breast MRI**, an **AI system reduced false-positive diagnoses by 27%** and **reading variability among radiologists by 25%** for suspicious lesions, addressing a major driver of unnecessary biopsies.



Source: (482).

W38

Despite demonstrated advantages, AI screening tools perform inconsistently across demographic groups. This is because these tools have been trained predominantly on datasets that lack the diversity of the US patient population. A systematic review of 41 studies evaluating mammography-based AI models for future breast cancer risk prediction found that White women were most represented across nearly every study, and fewer than one-third of the studies validated their findings using datasets other than those used to train AI models, limiting generalizability of findings (486). Similarly, researchers are finding substantial variability in accuracy and consistency in large language models—a type of AI trained on large text datasets to understand and generate human-like language (see **Sidebar 46**, p. 167)—for clinical decision-making, further underscoring the need for rigorous validation before use in the clinic (487).

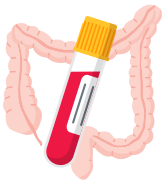
Studies have shown that patients' views on the use of AI in screening diverge significantly between demographically diverse populations. As one example, safety-net hospital patients—who are more likely to be from racial and ethnic minority groups and have lower income and education—were more likely to express lower trust in AI-assisted interpretation of screening mammograms than academic hospital patients (488). Experts emphasize the pivotal need for all stakeholders to work together in building safeguards, including the use of training data from diverse populations and rigorous validation, that will increase trust in AI-assisted screening tools and prevent these tools from further widening existing screening disparities (489).

Advances in Minimally Invasive Screening Approaches

Cancer screening tests are medical procedures that carry potential harm (see **Tests for Cancer Screening**, p. 86). Some, such as colonoscopy, also carry cultural stigma in certain population groups. These clinical and social factors can discourage eligible individuals from receiving the recommended cancer screening. Researchers are actively developing screening tests that are minimally invasive and have comparable sensitivity and specificity in detecting cancers early.

Minimally invasive tests analyze materials shed by tumors, such as DNA, RNA, or proteins, from blood, urine, or other body fluids, without requiring tissue biopsy or other invasive approaches. Liquid biopsy is one such minimally invasive test with growing application in early cancer detection, particularly

In a study of 957 average-risk adults, a **blood-based liquid biopsy test detected colorectal cancer with 90% sensitivity** and **89% specificity**, including 95% of stage I and II tumors.



Source: (493).

W39

cancers without reliable screening tests. Researchers have recently developed a liquid biopsy assay that looks for tumor HPV DNA in the blood using whole-genome sequencing (490). In a study of 56 participants, this assay was used to examine plasma samples collected up to 10.8 years before diagnosis in patients who later developed HPV-associated oropharyngeal cancer, a cancer type for which no screening test is currently available. The assay detected tumor HPV DNA in blood up to 7.8 years before clinical diagnosis with 100 percent specificity (491). These findings show the feasibility of using circulating HPV DNA for early detection of HPV-associated oropharyngeal cancer and support the broader potential of liquid biopsy approaches for cancers that currently lack a screening test.

The incidence of early-onset CRC, defined as CRC diagnosed in individuals ages 18 to 49, is on the rise (see **Cancer in 2026**, p. 14). Although stool- and blood-based screening tests are available for CRC (see **Sidebar 23**, p. 87), these tests are not validated for detecting early-onset CRC, indicating a growing need for a reliable screening strategy for this cancer type. An international study developed and validated a panel of six circulating biomarkers for detection of early-onset CRC in 542 participants (492). The test detected early-onset CRC with 97.3 percent sensitivity for early-stage disease and maintained 87.5 percent specificity across all age groups under 50.

Another application of liquid biopsy tests is the simultaneous detection of multiple cancer types. These tests, called multi-cancer early detection (MCED) tests, are being developed and validated to evaluate their sensitivity and specificity in detecting multiple cancers. A review of 20 studies, involving nearly 110,000 participants and 19 different MCED tests, found that accuracy varied widely by test and study design. Most studies used confirmed cancer cases instead of screening-eligible individuals and thus should be confirmed through randomized clinical trials and real-world data. Furthermore, no studies reported a benefit for cancer early detection, mortality, or quality of life (494). The first randomized controlled trial of an MCED test enrolled more than 140,000 adults ages 50 to 77 across England who had no symptoms or history of cancer. Researchers evaluated annual screening over 3 years and, compared to standard screening, found a 16 percent increase in stages I and II diagnoses, including ovarian, esophageal, pancreatic, and liver cancers. Although the trial reported at least 20 percent fewer stage IV diagnoses in screening rounds two and three, it did not meet the primary goal of reducing combined stages III and IV cancer diagnoses (495).

The NCI Vanguard study has established the infrastructure needed to rigorously assess MCED tests against current standards. NCI evaluated 23 technologically diverse MCED assays and has selected two MCED tests for inclusion in the Vanguard study, with the goal of informing the design of a randomized controlled trial for MCED testing (496). Researchers are also using modeling studies to project population-level benefit from MCED testing. One such study of 14 solid tumor cancer types, accounting for approximately 80 percent of US cancer incidence and mortality, projected that adding annual MCED testing to standard of care would lead to a 45 percent decrease in stage IV diagnoses compared to standard of care alone, with corresponding increases in stages I through III diagnoses (497). Another modeling analysis evaluating benefits and potential harms of blood-based CRC screening tests found that annual and biennial cell-free DNA strategies could be cost-efficient options for average-risk adults ages 45 to 75 (498). Together, these projections suggest that MCED testing, if validated in randomized controlled trials of screening-eligible individuals, could substantially change the landscape of cancer burden by detecting cancers at earlier, potentially curative stages (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 189).

Advances in Genomics-based and Risk-stratified Precision Approaches

Population-level cancer screening recommendations are primarily based on age and biological sex, with specific recommendations for individuals who are at higher risk of developing cancer, such as those with a family history of cancer, as was the case with **Carolyn Searles** (see p. 94) (see **Evidence Guides Cancer Screening Recommendations**, p. 84). Knowledge gleaned from cancer genomics not only is challenging this current approach but is also providing the basis for precision cancer screening recommendations.

In a study of more than 23,000 women without a personal history of breast cancer, researchers found pathogenic variants (PV) of genes associated with breast cancer in about 3 percent of the participants. Importantly, 30 percent of the women with PVs did not report a family history of breast or ovarian cancers that would have qualified them for genetic testing under the current guidelines (499). Conversely, in a study of nearly 68,000 women, those with a PV and a family history of breast cancer had an estimated 22.5 percent risk of breast cancer by age 50 and a 51 percent risk between ages 50 and 80.

continued on page 96

Carolyn Searles
AGE: 36 / WALLINGFORD, PENNSYLVANIA

Protecting Her Future Through Genetic Screening

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Carolyn Searles and her husband, Andrew, live in the suburbs of Philadelphia with their daughter and infant son. Carolyn, 36, was diagnosed with stage IIB triple-negative breast cancer in 2025. But her journey with cancer began years before her diagnosis.

In 2019, genetic testing showed that Carolyn's sister carried an inherited *BRCA1* mutation, which increases risk for a number of cancers, including breast and ovarian cancers. The finding prompted the entire family to undergo genetic testing. Carolyn, her other sister, and her father also tested positive, explaining the family's history of cancer. Her father had prostate cancer, and her aunt had been diagnosed with triple-negative breast cancer 3 times, starting at age 34.

Carolyn, who was 29 years old at the time, suddenly faced decisions she had never expected to make at such a young age. To understand her risks and options, she met with genetic counselors at Penn Medicine and began alternating mammograms and breast MRI scans every 6 months. At first, Carolyn hesitated about undergoing a preventive double mastectomy; she wanted to have children one day and knew that the surgery would mean she could not breastfeed.

Two years later, however, her best friend's diagnosis with inflammatory breast cancer created a new sense of urgency. "I felt like my body was a ticking timebomb, and if I could do something, I should," Carolyn recalled. She chose to undergo a preventive double mastectomy in November 2021.

Life moved forward. Carolyn and Andrew married in 2022, and their daughter, Corinne, was born the following year. After facing fertility challenges when trying to have a second child, they were overjoyed to learn that they were expecting a son through *in vitro* fertilization.

Then, just after Carolyn's 36th birthday, she discovered a golf ball–sized lump in her armpit. Within days, an ultrasound and biopsy confirmed stage IIB triple-negative breast cancer, an aggressive subtype often associated with *BRCA1* mutations. "The world stopped," she recalled.

The next day, as Carolyn sat holding ultrasound images of her healthy baby boy, her physician told her, "Your baby's fine. His organs are formed. You can receive chemotherapy. You can have surgery. You can do everything but get radiation." A team of specialists worked together to develop a treatment plan. Carolyn started chemotherapy within 2 weeks of diagnosis, and the tumor began shrinking within a week of her first infusion.

Throughout treatment, Carolyn received tremendous support. Family and friends helped with meals, childcare, and transportation, allowing her to continue working full-time while keeping life as normal as possible for her family.

To ensure that her son's development was not affected, Carolyn's physicians carefully timed her treatment. At 33 weeks and 4 days of pregnancy, Carolyn was induced and her son, Blake, was born healthy. Soon after giving birth, she resumed chemotherapy and began treatment with the immunotherapy pembrolizumab (Keytruda). Between appointments, she held her newborn in the neonatal intensive care unit whenever she could. "Cancer took a back seat because I had something beautiful to keep me going," she said.

After completing chemotherapy, Carolyn underwent mastectomy completion surgery to remove tissue that remained after the original surgery. Follow-up testing showed a pathologic complete response, with no signs of cancer in the tissue removed during surgery. Today, she is in remission while continuing immunotherapy. "I feel more and more like myself every day," she said. "Now I'm just a full-time working mom of 2 and trying to navigate that, which is a beautiful place to be."

Carolyn believes genetic testing changed her life years before her diagnosis. It allowed her to understand her cancer risk, access specialized counseling, and begin intensive screening. Because she carries a *BRCA1* mutation, Carolyn knows her journey is far from over. "I'll be relying on ongoing research to help identify the most effective strategies for ovarian cancer prevention," she said. Carolyn encourages anyone with a family history of cancer to learn whether genetic testing may be appropriate for them. "It's scary to know the truth, but knowledge is power," she said. "If there is something you can do to prevent cancer or reduce your risk, it's life-changing."

Drawing on her experience, Carolyn has lent her voice to advocacy efforts. She wrote to her member of Congress in support of the Constance C. McDaniel Medically Necessary Infant Formula and Donor Milk Act, introduced in May 2026 to help ensure access to infant formula or donated breast milk for mothers who medically cannot breastfeed.

Carolyn credits decades of research for giving her, Andrew, and their children a future together. Advances in genetic testing, risk-stratified screening for high-risk individuals, cancer treatment during pregnancy, and immunotherapy all played a role in her outcome. "Without research, my son and I might not be here today," Carolyn said. "I want members of Congress to know how important it is for me and my family to continue to fund research."

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

TABLE 4

Selected Active Clinical Trials of Vaccine-based Cancer Interception

Cancer Type	Patient Characteristics	Delivery Method	Study Phase	Launch Year	Target	NCT Number
Breast/Ovarian/ Pancreatic/Prostate cancer	*BRCA1/2* carriers	DNA-based	I	2021	hTERT, PSMA, WT1	NCT04367675
Breast cancer (DCIS)	HER2-expressing DCIS	Peptide-based	IB	2019	HER2 (4 degenerate HLA-DR epitopes)	NCT04144023
Colorectal cancer	Advanced polyps	Peptide-based	II	2014	MUC1	NCT02134925
Colorectal cancer	Lynch syndrome	Dendritic cell–based	I/II	2010	Small peptides from mutated proteins caused by faulty DNA repair/CEA	NCT01885702
Colorectal cancer	Lynch syndrome	Virus-based	II	2023	MUC1, CEA, Brachyury	NCT05419011
Pancreatic cancer	Germline *CDKN2A*/p16 mutations or family history, or the presence of a precancerous pancreatic cyst	Peptide-based	I	2022	KRAS mutants: G12D, G12R, G12V, G12A, G12C, G13D	NCT05013216
Smoldering multiple myeloma	Patients with confirmed smoldering multiple myeloma	Peptide-based	I	2017	XBP1, CD138, CS1	NCT02886065
Triple-negative breast cancer	*BRCA1/2/PALB2* carriers	Protein-based	I	2021	Alpha-lactalbumin	NCT04674306

BRCA1/2, breast cancer gene 1/2; CD138, cluster of differentiation 138 (Syndecan-1); *CDKN2A*, cyclin dependent kinase inhibitor 2A; CEA, carcinoembryonic antigen; CS1, cell surface signaling antigen 1; DCIS, ductal carcinoma *in situ*; HER2, human epidermal growth factor receptor 2; HLA-DR, human leukocyte antigen-DR isotype; hTERT, human telomerase reverse transcriptase; KRAS, Kirsten rat sarcoma viral oncogene homolog; MUC1, mucin 1; NCT, national clinical trial; *PALB2*, partner and localizer of BRCA2; PSMA, prostate-specific membrane antigen; WT1, Wilms tumor 1; XBP1, X-box binding protein 1.

Source: (510).

In comparison, the risk of breast cancer in women with a PV but no family history was about 9 percent by age 50 and 30 percent between ages 50 and 80 (500). Together, these findings indicate that screening criteria based only on one or two factors could exclude individuals who should be screened and highlight the need for combined assessment of genetic predisposition and other risk factors to develop precision strategies for cancer screening and prevention.

Large, randomized screening trials are evaluating the benefits of individualized cancer risk prediction compared to the current population-level criteria based on age and biological sex. One such trial with more than 28,000 women ages 40 to 74 enrolled found that tailoring the frequency of breast cancer screening to a woman's individual risk using genetic, polygenic, and other clinical data as well as family history is as safe as annual mammograms (501). Compared to the recommended annual screening mammograms, risk-adapted strategy found just as many advanced cancers, used significantly fewer mammograms overall, and directed the most intensive screening to the women who needed it most (501). These findings are further corroborated by a modeling study showing that, compared to annual mammogram screening, risk-adapted breast cancer screening would be associated with 6 percent more breast cancer deaths averted and 13 percent fewer false-positive findings (502).

Evidence in favor of risk-adapted screening strategies is also accumulating for other cancer types. For example, a recent study focused on lung cancer screening compared the NELSON criteria—which are based on age, smoking history, and recency of smoking cessation—and the PLCOm2012 risk

prediction model—which calculates an individual's likelihood of developing lung cancer over the next 6 years using a combination of factors, such as age, smoking history, body mass index, family history, diagnosis of chronic obstructive pulmonary disease, education level, and others. Researchers found that the PLCOm2012 risk prediction model identified 97 percent of lung cancers compared to 77 percent under the NELSON criteria (503). Similar risk-adapted approaches are proving effective in developing precision screening strategies for cancer predisposing syndromes (e.g., Lynch syndrome), prostate cancer, and smoldering multiple myeloma (504-506).

While risk-adapted screening strategies are proving to be as effective or more effective compared to the current recommendations, it is vital to address the potential of these strategies to exacerbate screening disparities. For example, researchers found that removing race and ethnicity from a breast cancer risk model—a strategy proposed to mitigate algorithmic bias—reduced identification of Black women at an intermediate or high risk of developing advanced breast cancer from 75.3 percent to 47.5 percent (507). These findings underscore the need for more research, inclusive of diverse populations, before such approaches can be implemented at the population level.

Genomics-based cancer early detection and risk stratification are enabling cancer interception, a strategy to stop, or intercept, precancerous states of cells before they develop into cancer (508). For example, individuals with Lynch syndrome have a significantly heightened risk of developing certain types of cancer because of mutations in genes involved in DNA repair. In a clinical trial involving 45 people with Lynch syndrome, researchers tested a messenger RNA (mRNA)–based vaccine (see **Cancer Vaccines**, p. 173), called Nous-209, designed to train the immune system to recognize and attack cells carrying gene mutations associated with Lynch syndrome. The vaccine was safe, caused no serious side effects, and triggered a strong, durable immune response. These findings are a promising early indication that vaccination may one day prevent cancer in people with inherited gene mutations that increase their likelihood of developing cancer (509). In addition to mRNA-based vaccines, several other cancer interception approaches are at various stages of clinical testing (see **Table 4**, p. 96).

A meta-analysis of six studies involving more than 6,100 women with *BRCA1* and *BRCA2* gene variants found that risk-reducing bilateral mastectomy—surgical removal of both breasts—was associated with a 62 percent reduction in overall mortality and a significant reduction in breast cancer–specific mortality among *BRCA1* gene carriers (511). Together, findings discussed in this section point to an exciting future of precision-based approaches for the early detection, prevention, and interception of cancer. Additional research is needed to ensure that these innovative and cutting-edge approaches are accessible and applicable to all segments of the population.

Progress Across the Clinical Cancer Care Continuum

IN THIS SECTION, YOU WILL LEARN:

- Researchers are leveraging insights into the cellular and molecular drivers of cancer development to design innovative, patient-centric clinical trials that lead to safer and more effective treatments.
- Advances in novel approaches to surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—the five pillars of cancer treatment—are saving and improving lives.
- From July 1, 2025, to June 30, 2026, the United States Food and Drug Administration (FDA) approved 11 new therapeutics for treating various cancer types, a new device for treating pancreatic cancer, and expanded the use of five previously approved anticancer therapeutics to treat additional cancer types.
- Among FDA approvals are the first molecularly targeted therapy for a rare, aggressive brain tumor with a specific genetic alteration, the first molecularly targeted therapeutic approved for patients with breast cancer that works by harnessing the cell's protein disposal system, the first immune checkpoint inhibitor for ovarian cancer, and the first chimeric antigen receptor (CAR) T-cell therapy for patients with marginal zone lymphoma.
- While these exciting new advances have the potential to transform patient care, much work is needed to ensure all patient populations have access to these treatments.

In the United States (US), the overall cancer death rate is declining steadily, and more individuals are living longer and fuller lives after a cancer diagnosis (see **Cancer in 2026**, p. 14, and **Advancing Cancer Survivorship Care**, p. 144). This progress is attributable, in part, to the rapid advances in cancer treatment propelled by breakthroughs across the continuum of medical research. Advances in cancer treatment and improved access to care are estimated to have prevented nearly 174,000 cancer deaths in the United States between 2010 and 2019 (3).

According to NCI, a **biomarker is a biological molecule** (e.g., DNA, RNA, or protein) **found in blood or other body fluids or tissues** that is a sign of a normal or an abnormal process, or of a disease such as cancer. A biomarker **may also be used to see how well the body responds to treatment**.

W40

Medical Research

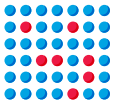
Medical research is an iterative process that is set in motion when a discovery with the potential to affect the practice of medicine or public health is made in any area of research or clinical practice (see **Figure 4**, p. 35). One way that researchers build on a discovery is by asking questions that can be tested through experiments in a wide range of models that mimic healthy and diseased conditions. Results from these experiments can lead to the identification of a potential preventive intervention or therapeutic target, or to the identification of a potential biomarker that can predict how a cancer might behave or how well a treatment might work. They also can feed back into the medical research cycle by providing new discoveries that lead to more questions or hypotheses.

SIDEBAR 25

Therapeutic Development

Target validation

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

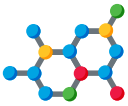


Drug screening

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

Lead identification

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



Lead optimization

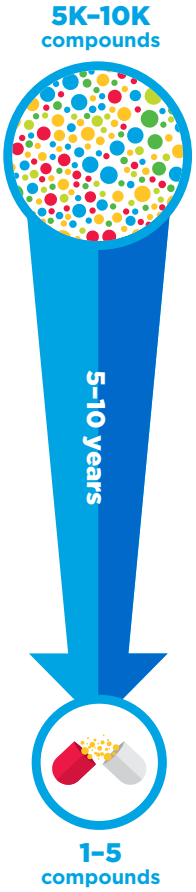
The characteristics of lead compounds are optimized to enhance potency and drug-like properties and to reduce side effects by enhancing specificity.

Preclinical testing

The optimized lead compound or compounds 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 or compounds are considered clinical candidates.

Investigational new drugs

One or more clinical candidates are generated through good manufacturing practices and assessed in rigorous good laboratory practice studies before submission to FDA for approval to use in clinical trials.



If a potential therapeutic target is identified, it takes many more years of preclinical research before the most promising candidate therapeutic is ready for testing in clinical trials (see **Sidebar 25**, p. 99). During this time, several candidates are rigorously tested to identify any potential toxicity and to determine the appropriate doses and dosing schedules for testing in the first clinical trial.

Clinical Research

Clinical research, also known as clinical studies or clinical trials, evaluates the safety and efficacy of candidate agents before they can be approved by the US Food and Drug Administration (FDA) and used as part of routine patient care. 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. Clinical studies in which participants are randomly assigned to receive an investigational agent or the standard care are called randomized clinical trials and are considered the most rigorous.

Clinical trials are vital for progress against cancer because they translate medical discoveries into meaningful advances in patient outcomes. Therapeutics that constitute today's standard of care are the direct result of discoveries and evidence generated through past clinical trials. Cancer treatment trials conducted by the Children's Oncology Group, along with high engagement of pediatric patients in those trials, drove dramatic improvements in outcomes, increasing 5-year survival rates for children with cancer from less than 60 percent in the mid-1970s to greater than 80 percent in the 2000s (512). Similarly, clinical trials conducted over the past decade for previously intractable cancers in adults, including advanced non–small cell lung cancer (NSCLC) and melanoma, have led to transformative improvements in clinical practice and patient outcomes (513).

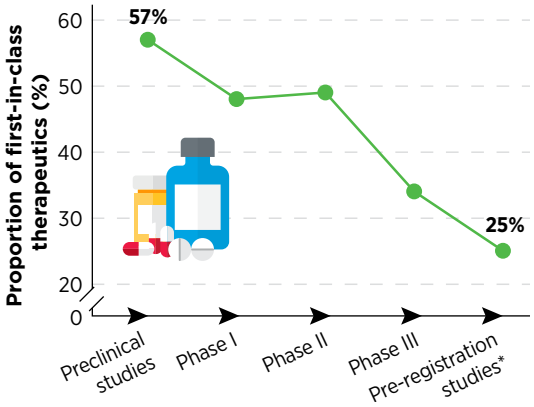
BETWEEN 2019 AND 2024, FDA APPROVED

NEARLY 200 NEW CANCER TREATMENTS

Based on evidence from nearly 200 clinical trials, these approvals included **both novel therapeutics and new uses for existing therapeutics**.

Source: (514). W41

An analysis of **investigational and FDA-approved cancer drugs** since 2011 found that **most late-stage candidates in the clinical pipeline did not have novel targets**. The proportion of first-in-class anticancer therapeutics—the first approved therapeutic against a novel cancer-causing target—declined with advancing clinical development.



* Studies conducted to support regulatory submissions.

Source: (518). W42

Participating in a clinical trial has many benefits. These include access to the latest and potentially more effective treatments before they are widely available, active involvement in making health care decisions, and a direct contribution to lifesaving cancer research for future patients (515). Institutional review boards critically evaluate and approve the design of all clinical studies before they can begin, and trials are carefully monitored throughout their duration. Patient safety and understanding of the clinical trial are prioritized through the informed consent process, which involves a discussion between the clinical research team and the patient about the trial's purpose and what is expected of the patient, potential benefits and risks, alternative treatments, and the patient's right to withdraw at any time.

Clinical trials evaluating potential new cancer treatments have traditionally been conducted in successive phases, each involving more patients and typically focusing on a specific cancer type (e.g., breast cancer or prostate cancer). Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how patients process it, and potential toxicities. Historically, phase I trials were not designed to evaluate the anticancer efficacy of a therapeutic. However, because of rapid progress in medical research, including clinical trial design and conduct, researchers are increasingly able to incorporate a preliminary evaluation of efficacy from phase I trials (516). Thanks to extraordinary advances in our understanding of cancer biology, patient responses to investigational therapies in phase I studies have also nearly doubled over the past two decades (517).

Phase II trials are designed to determine the initial efficacy of investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to current standard of care; when successful, the results of these trials have traditionally been used by FDA to approve new therapeutics or new indications for previously approved therapeutics. Phase IV trials are conducted after a therapeutic is approved by FDA and provide additional effectiveness or real-world data on the therapy. Sometimes phase 0 clinical studies are performed prior to traditional clinical trials wherein low doses of potential therapeutics are administered to a small number of patients to determine whether such treatments may have the desired effect.

The traditional, cancer-specific, multiphase clinical trial process requires large numbers of patients and takes many years to complete. However, this approach is not well suited to the current molecular era—in which the genetic alterations that drive cancer are being identified with greater precision and frequency (see **Sidebar 7**, p. 40), and therapies designed to target those alterations are being actively evaluated in clinical trials. Identifying and implementing more efficient clinical development strategies are areas of extensive investigation.

Innovations in Cancer Clinical Trials

Advances in cancer genomics and related technologies are transforming clinical trials by providing deeper insight into the molecular drivers of cancer and enabling researchers to identify patients most likely to benefit from specific therapies. As a result, clinical research is also evolving from the traditional tissue-based trials to a biomarker-driven and tissue-agnostic approach that involves treating cancers based on shared molecular targets rather than their site of origin in the body. Research shows that innovative designs, such as adaptive trial design (see **Sidebar 26**, p. 101), can increase efficiency and the likelihood of success of clinical trials (519).

SIDEBAR 26

A New Age of Cancer Clinical Trials

Recent advances in our understanding of genetic, epigenetic, immune-related, and other biological drivers of cancer have led to novel ways of designing and conducting clinical trials (520). Among the new concepts and designs for clinical trials that have emerged in recent years are the following:

Master protocols

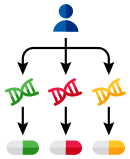
Also known as **main protocols**, refer to an overarching trial design that can answer multiple clinical questions. By allowing the evaluation of multiple new agents simultaneously and by matching the right therapeutics with the right patients earlier, master protocols reduce the number of patients who need to be enrolled in the trial and decrease the length of time it takes for a new anticancer therapeutic to be tested, approved, and made available to patients.
Example: DART study (521).

BASKET TRIALS

Aim 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.
Example: NCI-MATCH clinical trial (522).

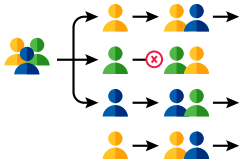
UMBRELLA STUDIES

Aim to identify the best therapy against different types of genetic mutations all within the same anatomic cancer type.
Example: Lung-MAP clinical trial (523).



PLATFORM TRIALS

Aim to assess multiple interventions against a disease and modify aspects of the trial design, if needed, by leveraging the accumulating data, thereby increasing the efficiency of the clinical research process. For example, this design allows researchers to terminate ineffective interventions or add new interventions during the study.
Example: RECOVERY trial for COVID-19 (524).

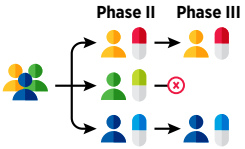


Adaptive trial designs

Permit pre-planned modifications based on interim data, such as reallocating patients to more effective treatment arms, adding or dropping treatment arms, modifying dosage, or stopping the trial early.
Example: I-SPY trial (525).

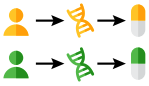
Seamless designs

Combine different phases of trials (labeling depends on the phases combined, e.g., phase I/II or phase II/III), allowing for seamless transition from preliminary to confirmatory studies and combined data collection. This design can reduce costs and permit research questions to be answered more quickly or with fewer patients. By enabling earlier access to robust efficacy and safety data within a single continuous study, seamless trial designs can allow FDA to approve promising new therapies without waiting for traditional, large phase III trials.
Example: CodeBreaK 100 phase I/II trial (526).



N of 1 clinical trial designs

Patient-centered approaches that provide a unique therapy to each patient based on their tumor profiles.
Example: I-PREDICT study (527).

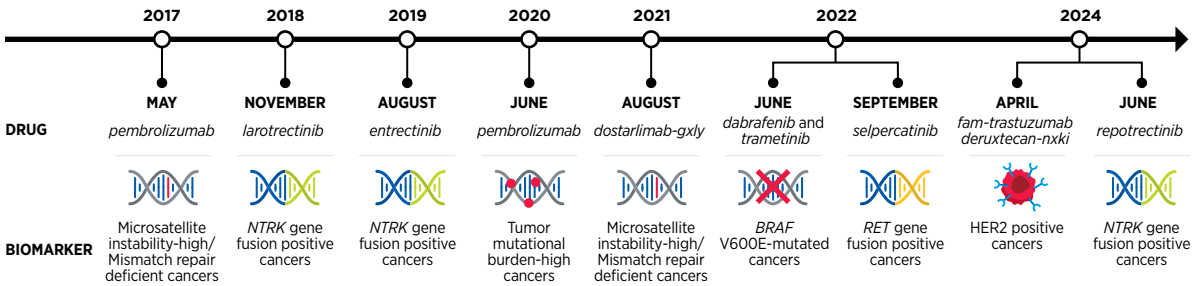


Many of the novel trial designs described above utilize **Bayesian methodology**, which allows researchers to adapt studies based on information that accrues during a trial, potentially allowing for smaller but more informative trials and for patients to receive better treatment.

CodeBreaK 100 (clinical trial evaluating KRAS G12C inhibitors); DART, Dual Anti–CTLA-4 and Anti–PD-1 Blockade in Rare Tumors (study); I-PREDICT, Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (study); I-SPY, Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis (trial); Lung-MAP, Lung Cancer Master Protocol (clinical trial); NCI-MATCH, NCI Molecular Analysis for Therapy Choice (clinical trial); RECOVERY, Randomized Evaluation of COVID-19 Therapy (trial).

FIGURE 16

Timeline of Tissue-agnostic FDA Approvals of Cancer Treatments



A watershed moment in cancer medicine was the May 2017 FDA approval of the immunotherapeutic pembrolizumab for treating patients with solid tumors not of a specific organ or tissue type but rather characterized by the presence of either of two specific molecular characteristics, or biomarkers, called MSI-h (microsatellite instability-high) and dMMR (deficient mismatch repair). 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 to treat cancer based solely on its molecular alterations and was the result of decades of research in cancer and the immune system along with innovations in clinical trial design and conduct. Subsequently, in November 2018, FDA approved the first molecularly targeted therapeutic, larotrectinib, to treat cancer based on the presence of a specific genetic biomarker known as *NTRK* gene fusions, which are identified in a diverse array of cancers in adults and children. As of June 30, 2026, nine therapeutics have received tissue-agnostic approvals from FDA for treating patients with any solid tumors that have specific genetic alterations. In addition, the 2021 FDA approval of belzutifan for cancers of the kidney, brain, and pancreas associated with von Hippel-Lindau syndrome, which is an inherited disorder, and the 2022 FDA approval of pemigatinib for myeloid/lymphoid neoplasms, a small group of blood cancers, reflect the site-agnostic concept, although each is limited to a defined group of cancer types.

Biomarker-driven clinical studies, which evaluate therapies in patients regardless of the site of their cancer's origin, are more often being used to support tissue-agnostic regulatory approvals for all tumors that have the targeted biomarker. As of June 30, 2026, nine therapeutics have received tissue-agnostic approvals from FDA for treating patients with solid tumors that have specific genetic alterations (see **Figure 16**, p. 102). However, emerging evidence suggests that successfully matching patients to biomarker-directed therapies is more complex than simply identifying a targetable alteration, with factors such as prior treatments, co-occurring molecular alterations, and tumor site of origin also influencing treatment response (528-530).

Clinical researchers are increasingly adopting more patient-centric trial designs in which the appropriate investigational agents are identified for each patient based on the unique features of their cancers. This is a shift from the traditional approach, in which patients were identified to fit in with an investigational therapy. Other key strategic changes being deployed include ongoing monitoring of tumor characteristics, including dynamic changes in the cancer cells, the tumor microenvironment, and the patient's immune system throughout clinical care, rather than a single assessment at the start of the study as was done traditionally. Researchers are leveraging tools such as advanced gene sequencing, liquid biopsies, and digital health technologies to monitor treatment efficacy and emerging resistance, guide treatment adaptation over time, and evaluate clinical outcomes.

Collecting multidimensional data over time enables researchers to adapt treatment regimen, dosage, or other aspects of the clinical trial protocol to more effectively manage treatment resistance. For example, researchers may decide, based on emerging molecular alterations, that combination therapy targeting multiple cancer drivers may be more effective. Supporting this approach, data from a recent precision oncology clinical trial in metastatic cancers demonstrated that a typical tumor harbored five pathogenic alterations and that patient outcomes improved when a greater number of these alterations were targeted with combinations of molecularly targeted therapeutics (527). The study also

FDA has developed several evidence-based strategies to expedite assessment of novel therapeutics for life-threatening diseases such as cancer.

One example is the **accelerated approval of a therapeutic** based on a surrogate clinical endpoint **that can reasonably predict a drug's effectiveness sooner**.

Any therapeutic approved in this way **must undergo additional clinical research** to verify that it provides patient benefit before it receives regular approval.

A recent study examining the real-world outcomes of patients with solid tumors who were treated with therapeutics that received accelerated approval found **improved outcomes for many drugs approved through this pathway** compared to standard treatments.

Source: (531). W43

represents a blueprint for an innovative personalized N of 1 clinical trial design for evaluating previously unexplored therapeutic combinations.

In looking to the future, the design and conduct of clinical cancer research need to keep pace with the new wave of scientific and technological advances. For example, precision medicine clinical trials must consider novel dosing strategies, optimal timing of therapeutic applications, and novel data collection methods. Traditionally, clinical trials have focused on identifying the maximum tolerated dose of a treatment. This strategy was suited for older cytotoxic chemotherapeutics but is potentially harmful when applied to molecularly targeted therapeutics and immunotherapeutics, since higher doses may increase toxicity without improving efficacy and can negatively affect patients' quality of life. In response, FDA has launched an evidenced-based initiative, Project Optimus, to reform dose optimization (see **Applying Regulatory Science to Ensure Safe and Effective Cancer Therapies**, p. 185) (532).

Currently, many precision medicine options are evaluated in late-stage cancer, once standard treatments have failed. However, there is increasing evidence that supports applying these therapies earlier, even as the first line of treatment after diagnosis to achieve maximal benefit for patients. Identifying the optimal timing in the course of cancer treatment when precision medicine is most effective and determining the optimal sequence of treatments—for example, whether delivering molecularly targeted therapeutics or immunotherapeutics prior to surgery can improve surgical outcomes and survival—are key areas of ongoing clinical research.

Another shortcoming that has restricted the scope of current clinical research is the underutilization of rapidly accumulating vast amounts of nonclinical and clinical data generated through research and clinical practice. Leveraging existing knowledge from publicly available, open-access repositories such as chemical and drug databases, published literature, patient registries with clinical or genomic data, real-world data, electronic health records, past clinical trial data, and patient reported outcomes is pivotal to driving meaningful progress and transforming the future of cancer clinical trials (533). It is also important that researchers identify effective and ethical ways to share clinical data, biospecimens, and biospecimens-related data to accelerate clinical cancer research and maximize their impact on patient outcomes (534).

Artificial intelligence (AI), including machine learning tools, is beginning to help researchers harness diverse datasets to further improve clinical trials. AI tools are increasingly being used in clinical research to identify patients eligible for trials; predict which patients are most likely to benefit from experimental treatments; simulate how new therapeutics may work in a patient using digital twins; create synthetic control groups by leveraging past patient data and thereby allowing more trial participants to receive the new investigational therapy; and assess how well trial results apply to real-world patient populations (see **Envisioning the Future of Cancer Research**, p. 166) (535-539). However, there are limitations to the current use of AI, including lack of diversity in training data and proper regulatory oversight, that must be overcome before these tools can become a part of regular clinical practice.

Low participation rate and a lack of sociodemographic diversity among those who do participate are two of the most pressing challenges in cancer clinical trials (see **Sidebar 27**, p. 104). Based on recent estimates, only 7 percent of adult cancer patients in the United States participate in clinical trials (540). As a result, many studies fail to enroll enough patients to draw meaningful conclusions about the effectiveness of the investigational therapeutic. In this regard, a recent study reported an increase from 2013 to 2023 in the percentage of phase II clinical trials for which enrollment issues were cited as a reason for study termination (541).

Clinical trial participants often do not reflect the broader population of patients receiving cancer care in the United States (542). Individuals who participate in clinical trials tend to be younger, healthier, and less racially, ethnically,

SIDEBAR 27

Disparities in Cancer Clinical Trial Participation

To ensure that investigational 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 in the United States. Despite this knowledge, several segments of the US population are underrepresented in clinical trials because of multifactorial barriers to participation. Examples of these disparities include the following:

ONLY 4% participate	Based on recent estimates, only 4 percent of patients treated at community cancer clinics participate in clinical trials, compared to greater than 20 percent treated at large, urban academic research institutions (540).
ONLY 6% reported	A review of 471 clinical trials evaluating immune checkpoint inhibitors—one of the most transformative advances in cancer therapy—demonstrated that race was not reported in 31 percent and ethnicity in 59 percent of studies, and only 6 percent reported race- or ethnicity-specific outcomes. White patients were overrepresented, whereas Black and Hispanic patients were underrepresented relative to their disease burden in the United States (545).
RARELY included	Native Hawaiian or Pacific Islander patients were rarely included or even identified in clinical trials for cancer therapeutics approved between 2006 and 2021 (546).
More than 70%	An analysis of phase III clinical trials evaluating interventions for acute myeloid leukemia (AML) from the past decade showed that more than 70 percent of participants were less than 65 years old, despite AML being a disease primarily encountered in older patients (547).
70% of US counties	A recent analysis of 6,710 clinical trials showed that more than 70 percent of US counties had no active cancer trials, reflecting a lack of local trial availability. The disparity was particularly pronounced in rural areas—86 percent of nonmetropolitan counties lacked trials, compared to 44 percent of metropolitan counties (548).
2.5 TIMES farther	Analysis of 30 years of data from 29,546 patients enrolled in cancer clinical trials conducted in the United States showed that rural patients traveled an average of 2.5 times farther than urban patients to access a trial, with nearly three in four rural participants traveling over 50 miles (549).
94% of all cancer clinical trials	Seventy-eight major US cancer centers that conduct 94 percent of all cancer clinical trials are located in areas that are socioeconomically more affluent and have higher proportions of White individuals compared to the national average (550).

and geographically diverse than the broader population of patients receiving cancer care in the United States. Diversity among clinical trial participants is critical because the efficacy and safety of an intervention may differ across populations—for example, among individuals from different ancestral backgrounds, age groups, or biological sexes.

Underrepresentation in clinical trials compromises the generalizability of trial findings to the real-world patient population. In recent years, FDA has decided not to approve cancer therapies if clinical trial participants were not representative of the US patient population, due to concerns regarding generalizability of findings (543,544).

Numerous challenges limit patient participation in cancer clinical trials. While some barriers operate at the individual level for patients and health care providers, most arise from suboptimal clinical trial design and the ways in which trials are implemented within the broader health care system. Investigation of the existing barriers that limit participation of racial and ethnic minority groups and other medically underserved populations in cancer clinical trials has identified financial challenges, inadequate or complete lack of insurance, medical distrust, implicit biases among health care providers, lack of clinical trial availability, overly restrictive eligibility criteria, and lack of community outreach and education efforts as major factors driving disparities in clinical trial participation (16).

As discussed in detail in the *AACR Cancer Disparities Progress Report 2026*, increased knowledge of the barriers is helping researchers, regulators, and policymakers design and implement evidence-based adaptations that can improve access to clinical research. For instance, financial resources, particularly income and property ownership, have been shown to be among the strongest predictors of clinical trial participation (38). Although the cost of study drugs and research-related expenses are usually covered by clinical trial sponsors, routine care costs must be covered by the patient's health insurance, and participants may still face out-of-pocket expenses for additional trial-specific activities. These findings have led researchers to evaluate the impact of financial navigation to improve participation in clinical trials. A recent study showed that monetary reimbursement for trial-related costs reduced financial strain among women with breast cancer, suggesting that this approach may improve patient retention in clinical trials (551).

Interventions aimed at addressing other structural and social drivers of health, such as modifying trial design to ease patient participation, expanding eligibility criteria, improving the efficiency of data collection, including patient reported outcomes, and engaging in community outreach and patient navigation, are also being evaluated. Additionally, researchers are leveraging AI and real-world data to increase clinical trial representation and diversity by improving patient matching, providing supplemental information on underserved populations, and increasing the generalizability of trial findings (552-554). Another critical area of focus for all stakeholders in medical research is to ensure that the clinical research workforce is representative of the patient population it serves.

FDA has been developing programs to modernize clinical trials and streamline the regulatory pathway, with the goal of accelerating drug development (see **Advances in Rigorous Clinical Trial Design**, p. 185). These include efforts to monitor safety signals and trial endpoints in real time to accelerate approval of promising therapies, leverage AI and data science, facilitate the use of Bayesian methodologies (see **Sidebar 26**, p. 101), eliminate regulatory burden, clarify phase-appropriate requirements, and build multisector partnerships to facilitate greater efficiency across the drug development continuum.

In addition, FDA is reinforcing requirements for clinical researchers to submit clinical trial results in a timely manner to help reduce publication bias, improve transparency, and ensure a more complete and accurate understanding of the safety and efficacy of medical products. Efforts were also underway to implement diversity action plans that would have required researchers and funders of clinical trials to submit concrete goals and needed steps for enrolling specific demographic groups in pivotal studies used by FDA to make regulatory decisions on new drugs. However, policy changes from the current Administration have jeopardized progress in this critical area.

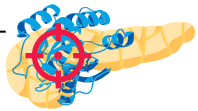
The COVID-19 pandemic, despite its adverse effects on many aspects of cancer research and patient care, enabled

Expanded Access

FDA's Expanded Access, or "compassionate use," program **allows patients with serious or life-threatening diseases to receive investigational treatments outside of clinical trials** when no satisfactory approved treatment options are available.

To qualify, patients must be unable to enroll in a clinical trial, and the potential benefits of treatment must outweigh the risks without compromising the drug's ongoing clinical development.

MAY 2026



FDA allowed expanded access for the investigational pancreatic cancer drug daraxonrasib. Daraxonrasib is a molecularly targeted therapeutic designed to inhibit the RAS protein that is mutated in most pancreatic cancers.

FDA's decision was based on the results from a phase III clinical study in which patients with advanced pancreatic cancer who received daraxonrasib survived twice as long as those who received standard chemotherapy.

Source: (555). W44

Globally, less than 5% of cancer patients participate in clinical trials.

Nearly 90% of all clinical trials are conducted in high-income countries and regions, including the United States, China, Japan, and Europe. **Low participation is particularly pronounced in low-income and middle-income countries, where access to trials is limited.**

A review of the World Health Organization's International Clinical Trials Registry Platform showed that greater than 81% of pediatric cancer trials are located in high-income countries. **Trials in low-income and middle-income countries are more often conducted by single institutions** and concentrated on supportive care.

Sources: (71,560,561). W45

researchers to decentralize certain aspects of clinical trials so that lifesaving therapeutics could be brought quickly to as many patients as possible (556). Adaptations implemented during the pandemic, including consenting patients remotely, permitting telehealth for routine clinical assessments, delivering experimental drugs to patients, and allowing the use of local laboratory, imaging facilities, or community health centers accessible to patients, offered a blueprint to further reform clinical trials for the benefit of patients. It is, therefore, not surprising that the number of decentralized trials rose sharply beginning in 2020, following only modest growth from 1998 to 2019 (557).

Emerging data indicate that decentralized and patient-centric clinical trial approaches may be associated with increased access to participation and greater representation of rural and other medically underserved patients (558). Similar efforts are underway across large health care systems such as the US Department of Veterans Affairs' Veterans Health Administration (VHA) to expand trial availability, improve referral pathways, and address logistical barriers to increase veteran access to cancer clinical trials (559). Ongoing research must continue to evaluate the impact of decentralized approaches on advancing clinical research and improving patient outcomes.

Progress Across the Pillars of Cancer Treatment

Research discoveries made as a result of innovative cancer science are continually being translated into new medical products for cancer prevention, early detection, diagnosis, and treatment. Approval of new medical products, including new anticancer treatments, is not the end of a linear research process. Rather, it is an integral part of the medical research cycle because observations made during the routine use of new medical products can help to accelerate the pace at which similar products are developed and to stimulate the development of new, more effective products.

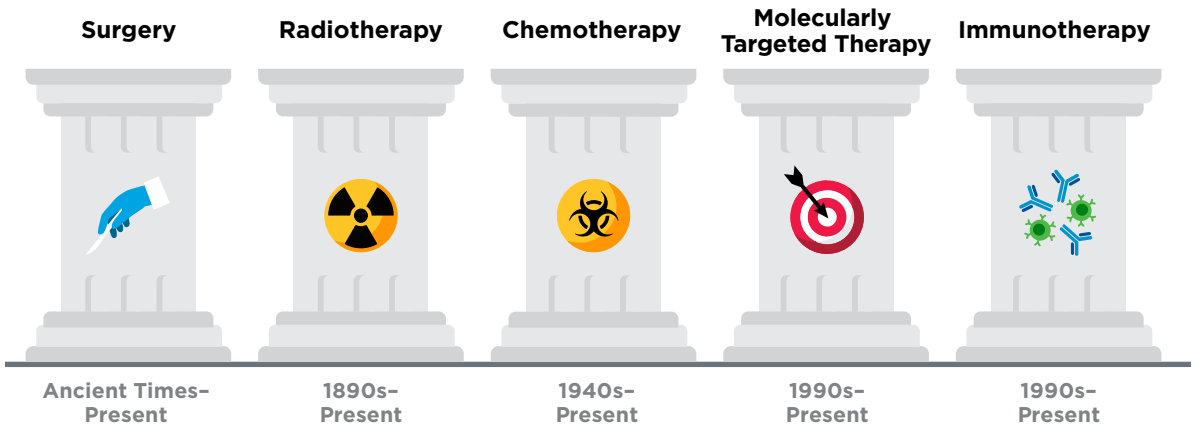
Traditionally, newly approved therapeutics are utilized alongside treatments already in use, including existing surgeries, radiotherapies, and chemotherapies, all of which continue to be the mainstays of clinical cancer care (see **Figure 17**, p. 107). In recent years, the rapid rise of molecularly targeted therapies and immunotherapies—the two newest pillars of cancer treatment—has ushered in a new era of personalized cancer medicine. However, researchers are continually evaluating new ways to refine the use of surgery, radiotherapy, and chemotherapeutics to improve survival and quality of life for patients. Additionally, efforts are underway to determine whether lifestyle factors, such as physical activity and dietary changes, as well as use of widely used medications, such as low-dose aspirin, can impact cancer treatment and outcomes (562-564).

The following sections focus on the recent advances across the five pillars of cancer treatment, in particular, the 11 new anticancer therapeutics approved by FDA in the 12 months spanning this report, July 1, 2025, to June 30, 2026 (see **Table 5**, p. 108). During the same time frame, FDA expanded the use of five previously approved anticancer therapeutics for treating additional types of cancer. Furthermore, FDA expanded the use of several previously approved therapeutics to include treatment at different timepoints in the course of clinical care or treatment of a different subtype of the same cancer. Comprehensive information on all anticancer therapeutic approvals can be found on FDA's website (565). Because many of these treatments, particularly molecularly targeted therapeutics and immunotherapeutics, are relatively new to the clinic, their long-term and late effects are still unknown (see **Advancing Cancer Survivorship Care**, p. 144). The fast pace of approval and increasing clinical use of these cutting-edge therapeutics warrant close monitoring of patients receiving such agents.

New medical products used across the continuum of clinical cancer care transform lives by extending survival and improving quality of life. However, not all patients in the United States receive the standard of care recommended for the type of cancer with which they have been diagnosed and for the stage of cancer at the time of diagnosis. Disparities

FIGURE 17

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. In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar. The foundations for the third treatment pillar—chemotherapy—were established in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and chemotherapy—continue to be critical components of cancer treatment. The introduction of the first molecularly targeted therapeutics in the late 1990s led to the establishment of the fourth pillar, molecularly targeted therapy. Also, in the late 1990s, decades of discovery in science laid the groundwork for the fifth treatment pillar, immunotherapy. 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.

in cancer treatment are driven largely by structural and socioeconomic factors, such as lack of access to health care facilities or health insurance, as well as high costs of cancer care (see **Sidebar 28**, p. 109). Research has shown that in the United States, disparities in survival for several cancer types can be eliminated when all patients have equivalent access to standard treatments (16). Some studies have found no racial or ethnic disparities in cancer outcomes among patients who are treated at a single-payer system, such as VHA, the nation's largest integrated health care system (566). In fact, based on a recent analysis, Black veterans with cancer receiving care through VHA had similar or better overall survival and cancer-specific survival compared to their White counterparts (567).

Medicaid expansion through the Patient Protection and Affordable Care Act (ACA) has been shown to increase insured status, early diagnosis, access to high-volume hospitals and timely cancer treatment, and to reduce cancer disparities, leading to improved outcomes for patients (568-570). As one example, Medicaid expansion was shown to improve surgical access and survival for patients with pancreatic cancer (571). However, improvements were delayed and uneven. Persistent disparities attributable to structural and social drivers highlight the need for all stakeholders in public health to work together and ensure equitable access to quality cancer treatments.

There are stark disparities in the cost and accessibility of cancer treatments around the world, with major differences between high-income and low-income countries (572). According to a recent analysis, patients in most high-income countries can access cancer medications without significant out-of-pocket expenditure, while in lower middle- and low-income countries, 40 percent of essential chemotherapeutics are only available at full cost (573). Recent disruptions to pharmaceutical transport routes associated with conflict in the Middle East highlight how fragile global supply chains can further threaten access to critical cancer medicines in low-income and middle-income countries (64).

Advances in Cancer Treatment With Surgery

For centuries, surgery was the only pillar of cancer treatment (see **Figure 17**, p. 107). Today, it remains the foundation

TABLE 5

Newly FDA-approved Anticancer Therapeutics (July 1, 2025–June 30, 2026)

Type of Treatment	Generic Name	Trade Name	What It Is	Approved For
MOLECULARLY TARGETED THERAPY	capivasertib*	Truqap	Cell-signaling inhibitor	Certain type of prostate cancer†
	▶ dordaviprone	Modeyso	Cell-lysis mediator	Certain type of brain tumor
	▶ imlunestrant*	Inluriyo	Antihormone therapy	Certain type of breast cancer
	▶ pivekimab sunirine-pvzy	Decnupaz	Cell-lysis mediator	Blastic plasmacytoid dendritic cell neoplasm, a type of blood cancer
	▶ relacorilant	Lifyorli	Antihormone therapy	Certain types of ovarian cancer
	▶ sevabertinib*	Hyrnuo	Cell-signaling inhibitor	Certain type of lung cancer
	▶ sonrotoclax	Beqalzi	Cell-signaling inhibitor	Certain type of lymphoma
	▶ sunvozertinib*	Zegfrovy	Cell-signaling inhibitor	Certain type of lung cancer
	▶ vepdegestrant*	Veppanu	Antihormone therapy	Certain type of breast cancer
	zenocutuzumab-zbco	Bizengri	Cell-signaling inhibitor	Certain type of biliary duct cancer†
	▶ ziftomenib	Komzifti	Gene transcription modifier	Certain type of leukemia
	▶ zongertinib*	Hernexeos	Cell-signaling inhibitor	Certain type of lung cancer
IMMUNOTHERAPY	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of stomach cancer†
	▶ linvoseltamab-gcpt	Lynozyfic	Bispecific T-cell engager	Multiple myeloma
	lisocabtagene maraleucel	Breyanzi	CAR T-cell therapy	Certain type of lymphoma†
	pembrolizumab*	Keytruda	Immune checkpoint inhibitor	Certain types of ovarian cancer†

▶ Denotes newly approved anticancer agents.
CAR, Chimeric antigen receptor.
* Approved with a companion diagnostic.
† Expansion for new indication.

of curative treatment for many patients. Surgery is used in several ways during the care of a patient with cancer (see **Sidebar 29**, p. 110).

Sometimes, additional therapy is given before, after, or around the time of surgery based on the specific features of a patient's tumor (see **Sidebar 30**, p. 111). Researchers have found that this approach not only improves the surgeon's ability to remove the tumor (e.g., by shrinking the tumor when given before the surgery) but also increases the patient's overall survival and/or quality of life (579). Researchers are continuously developing new strategies to maximize the benefits and minimize the harms of cancer surgery. These approaches include identifying patients who may benefit from less invasive procedures or safely forgo surgery without compromising outcomes, expanding surgical options for patients who were previously not considered ideal candidates based on emerging evidence, and incorporating digital technologies and other innovative tools to improve surgical outcomes.

As one example, a recent study showed that certain patients age 80 and older with early-stage NSCLC can safely undergo potentially curative surgery and achieve outcomes comparable to those in younger patients (580). These data are important because more adults age 80 and older will be diagnosed with cancer with an increase in life expectancy. Historically, these patients have been excluded from surgery and clinical trials due to concerns regarding comorbidities and treatment risks. The new findings demonstrate that when carefully selected based on their overall health, older patients can tolerate surgical procedures well and while they may experience some postoperative complications, the quality of life improved significantly over time.

SIDEBAR 28

Disparities in Cancer Treatment

Research is constantly powering the development of new cancer treatments that are saving and improving lives. However, medically underserved populations experience multilevel barriers to quality cancer care, attributable largely to structural and social inequities, and are less likely to receive recommended treatments. Examples of these disparities include the following:

MORE LIKELY to forgo surgical treatment	Patients from racial and ethnic minority groups are more likely to forgo surgical intervention for potentially curable malignancies; these differences have persisted over time and likely reflect structural and health system barriers (574).
LONGER DAYS to treatment	Patients with metastatic breast cancer from racial and ethnic minority groups experienced longer days to radiotherapy, chemotherapy, and molecularly targeted therapy initiation compared to White patients (575).
NEVER received systemic therapy	Among older adults diagnosed with metastatic non–small cell lung cancer between January 2006 and December 2021, almost half of patients never received systemic therapy, and the proportion treated only minimally improved over time (576).
SIGNIFICANTLY longer time to testing	Among patients with advanced or metastatic breast, prostate, colorectal, pancreatic, and lung cancers, those from low socioeconomic status, Black or Hispanic backgrounds, and covered by Medicaid or Medicare experienced significantly longer time to genomic testing compared to their respective reference groups (577). Genomic testing to identify targetable alterations in cancer forms the basis of precision medicine.
MORE LIKELY to receive immunotherapy	A large US study of more than 47,000 patients receiving treatment for advanced or metastatic melanoma demonstrated that the use of immunotherapy increased substantially between 2004 and 2021 and was linked to better survival, but access to these treatments was uneven (578). Patients with private insurance, living in neighborhoods with higher income and education, and those treated at academic centers were more likely to receive immunotherapy.

Digital health technologies are increasingly being incorporated into clinical care to make cancer treatments more patient-centric. A recent clinical study compared remote perioperative telemonitoring with standard care delivered by surgeons in patients with gastrointestinal, genitourinary, or gynecologic cancers (581). Patients receiving remote telemonitoring care used a wearable device and reported symptoms via a mobile application before and after surgery. When the reported data deviated from predetermined thresholds, patients were contacted by nurses. The study showed a 6 percent greater functional recovery rate among participants who received telemonitoring compared to usual care (581). While the benefit was modest, the finding supports further research to determine the optimal use of wearable sensor–based monitoring before and after surgery and to evaluate whether more intensive multimodal interventions, such as exercise and nutrition programs, can enhance symptom management and improve postoperative outcomes.

Minimizing the Use of Invasive Cancer Surgery

Several recent studies have shown that performing less invasive surgeries or avoiding surgeries altogether can benefit certain patients by minimizing tissue damage and postprocedural complications while maintaining, and in some cases

SIDEBAR 29

Using Surgery for Cancer Treatment

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

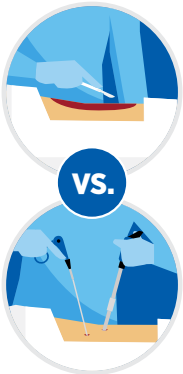
SURGERY TO STAGE CANCER is performed to determine how far the cancer has spread from the site of origin so that the best treatment plan can be developed for the patient.

SURGERY TO REMOVE CANCER is performed to remove the entire tumor and some surrounding tissue if cancer is confined to one area of the body.

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

SURGERY TO EASE PROBLEMS caused by cancer 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 is 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 is 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 inside the body onto a monitor, which allows the surgeon to see what is happening. Special surgical 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 an enhanced ability for surgeons to work within confined spaces.

improving, long-term outcomes (582-585). A few examples of such findings are discussed below.

The main purpose of neoadjuvant therapy is to shrink the tumor and reduce lymph node involvement before surgery, making it possible to perform a less extensive surgery. Based on a new report, the use of neoadjuvant therapy has significantly increased since 2010, particularly for pancreatic, gynecologic, and certain abdominal cancers (586).

Emerging data suggest that, in a small number of cancer types, carefully selected patients who have achieved a complete response, that is, those who have no detectable cancer, after neoadjuvant treatments (see **Sidebar 30**, p. 111), may be able to safely avoid surgery, although cancer recurrence remains possible and careful monitoring is essential. One area of increasing research focus is identifying patient groups who may be able to avoid surgery after showing strong responses to neoadjuvant immunotherapy. Early findings across several cancer types highlight the significant potential of this approach (587-589). Additionally, researchers are investigating biomarkers such as circulating tumor DNA (ctDNA) or isolated tumor cells that are present in lymph nodes to guide treatment decisions after surgery, for example, to decide whether patients need adjuvant treatments (590,591).

Many cancers spread through the body's lymphatic system, and one of the earliest sites of tumor spread is nearby lymph nodes, which are small round organs that are part of the lymphatic system (see **Blood and Lymphatic Systems**, p. 45). Lymph node dissection is a common procedure that involves removing lymph nodes near the tumor to determine whether the cancer has spread beyond the primary site, given the lymphatic system's role in metastasis. Lymph node dissection is routinely performed in patients with solid tumors, such as breast, head and neck, colorectal, stomach, or thyroid cancers.

There are two main types of lymph node dissection: regional, which targets nodes closest to the tumor, and extended (or radical), which involves a wider removal of lymphatic tissue, often across multiple nodal regions. While regional dissection helps with accurate staging and treatment planning, extended

SIDEBAR 30

Commonly Used Terms 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

The disappearance of all signs of cancer in response to treatment. The lack of all signs of cancer in tissue samples removed during surgery or biopsy after treatment with other approaches such as radiation, chemotherapy, immunotherapy, or a combination of these is called *pathologic complete response*.

Disease control rate

Percentage of patients whose cancer does not progress after a certain treatment period.

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.

Minimal residual disease

A very small number of cancer cells that may remain in the body during or after treatment. Also called measurable residual disease.

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

Length of time from start of treatment until disease progression or death. The length of time, after primary treatment for a cancer ends, that the patient survives without recurrence or death is called *disease-free survival*.

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.

Time to progression

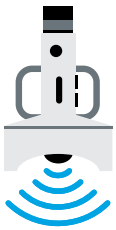
Time from the date of diagnosis or the start of treatment until cancer starts to get worse or spread to other parts of the body. Sometimes **time to next treatment**, defined as the time from initiation of one treatment until initiation of the next line of therapy, is used when progression is difficult to measure.

dissection carries a higher risk of complications. For example, axillary lymph node dissection (ALND)—an extended procedure historically performed when breast cancer was suspected to have spread to underarm lymph nodes—can lead to morbidity such as lymphedema, numbness, shoulder stiffness, and long-term functional limitations.

Several clinical trials have now demonstrated that ALND offers no survival benefit over regional dissection, also known as sentinel lymph node biopsy (SLNB), and can be safely omitted in certain early-stage breast cancer patients, including those with small tumors and normal lymph nodes on ultrasound imaging or those who respond well to neoadjuvant chemotherapy (592-594). Additionally, ongoing clinical studies are evaluating whether even certain higher-risk patients with limited metastasis to lymph nodes can safely forgo ALND (595). Moreover, researchers are finding that in selected low-risk patients even SLNB can be omitted without compromising outcomes (594).

Researchers are also evaluating whether less invasive procedures could replace traditional surgeries for some patients. A long-term follow-up of patients with certain types of pancreatic cancer who received either minimally invasive surgery or traditional surgery showed no significant difference in overall survival or disease-free survival between the two groups, supporting the safety and effectiveness of the less invasive approach (596). Minimally invasive surgery is associated with faster postoperative recovery and can be especially beneficial for patients with pancreatic cancer, facilitating earlier initiation and potentially better tolerability of adjuvant treatments. In another study, minimally invasive surgery was shown to be associated with improved outcomes compared to open surgery for patients with colon cancer (597).

Histotripsy is a noninvasive ultrasound-based treatment that uses sound waves to precisely destroy tumors while sparing nearby healthy tissues and may also stimulate the immune system to attack cancer.



The technology was approved by FDA in 2023 based on clinical data demonstrating that it **could destroy liver tumors**.

Emerging real-world data indicate that histotripsy **can provide effective short-term tumor control**, with 95 percent of treated liver tumors showing no evidence of viable cancer on imaging 30 days after treatment.

Sources: (600,601). W46

Tumor ablation is a minimally invasive treatment that destroys tumors in organs like the liver, kidney, bone, or lung using extreme heat, extreme cold, or other energy-based methods that damage cancer cells. A retrospective analysis that compared outcomes after ablation or surgical resection among patients with renal cell carcinoma, the most common kidney cancer, found that tumor progression following treatment did not differ between the two groups (598). However, patients who received ablation had fewer posttreatment complications and shorter hospital stays. Another recent study strengthened evidence supporting less invasive surgery for selected patients with pleural mesothelioma, a rare aggressive cancer arising in the thin tissue lining the lungs (599).

Improving Quality of Life After Cancer Surgery

Despite the immense benefits of surgery, complications are common and can negatively affect patients' quality of life. Programs to enhance recovery after surgery are emerging as one approach to address this issue. These multimodal, transdisciplinary programs focus on optimizing preoperative, perioperative, and postoperative patient care 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 can begin adjuvant treatment. Providing patients with an individualized prehabilitation plan that includes exercise, nutrition, stress reduction, and other behavioral modifications to optimize their physical fitness before surgery has been successful in improving patient outcomes.

According to a recent study in nearly 2,400 patients undergoing colorectal cancer surgery in the Netherlands, participation in a 4-week multimodal prehabilitation program that included high-intensity exercise, nutritional support, psychological counseling, and optimization of comorbidities was associated with a reduction in both surgical and overall medical complications, a shorter hospital stay, and reduced rates of hospital readmission and intensive care use (602). The benefits of the program were experienced by all patients regardless of age. Notably, basic research (see **Basic Research Decoding Cancer's Complexities**, p. 34) and preclinical studies have shown that preoperative exercise can enhance antitumor immune responses and prevent colorectal cancer metastasis (603).

Another clinical study from China demonstrated that a short, multimodal, prehabilitation program combining exercise, nutrition, psychosocial care, and other supportive interventions before surgery helped older adults with frailty better prepare for stomach cancer surgery. Patients who completed at least 2 weeks of prehabilitation before surgery experienced fewer postoperative complications, improved physical fitness before surgery, and recovered faster afterward, compared to those who received standard care alone (604).

Collectively, these findings suggest that helping patients improve their physical condition before surgery may reduce complications and improve recovery.

Advances 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. Radiotherapy plays a central role in the management of cancer and works primarily by damaging DNA, leading to cancer cell death.

Globally, 50 percent of all patients with a new diagnosis of cancer need radiotherapy as their initial treatment, and 15 percent require follow-up radiotherapy (605). Unfortunately, significant disparities exist in the access to radiotherapy. According to a recent report, sub-Saharan Africa has the fewest radiotherapy machines per patient—with around 20 countries lacking any—while North America has the highest availability (605). In high-income countries, there is one radiotherapy machine for every 130,600 people, compared to just one for every 15.6 million people in low-income countries (605). As cancer cases continue to rise globally, experts predict that by 2050, the need for trained radiotherapy professionals will grow by more than 60 percent (605).

There are many types of and uses for radiotherapy (see **Sidebar 31**, p. 114). However, it is important to note that radiotherapy may also have harmful side effects, in part, because of the radiation-induced damage to healthy cells surrounding the tumor tissue (606). Because of the central role of radiotherapy in the treatment and management of cancer, researchers are continually innovating radiotherapeutic approaches to maximize the benefits for patients while minimizing potential harm.

Long-term effects of radiation therapy can negatively impact a patient's quality of life. Researchers are evaluating approaches to make radiotherapy safer and more effective, including using biomarkers to identify patients who are unlikely to benefit from radiation or may be more vulnerable to its toxic effects, allowing radiotherapy to be reduced or even avoided without affecting patient outcomes (607,608). As one example, advances in radiation delivery techniques over the past several decades have dramatically reduced unintended radiation exposure to the heart and the associated risk of cardiovascular disease among women with left-sided breast cancer (609).

For women with early-stage breast cancer, surgery followed by radiotherapy had been the standard treatment, since it was believed that eradicating any remaining breast cancer cells with radiation after removal of the tumor would improve long-term outcomes. However, several studies have now shown that patients with early-stage breast cancer who are characterized as very low risk, based on certain molecular characteristics, can forgo radiation therapy after surgery without any excess risk of cancer recurrence, as long as they receive guideline-adherent treatment with hormone therapies (610-613).

Adding to this evidence, a recent clinical trial has now shown that certain patients even with higher-risk breast cancer can safely avoid radiation (614). The trial included more than 1,600 women with intermediate-risk breast cancer, defined as stage II disease with one to three positive lymph nodes or tumors with aggressive features but no lymph node involvement. Half of the patients received radiation therapy, while the other half did not. After 10 years of follow-up, overall survival exceeded 80 percent in both groups, with no significant difference between patients who received radiation and those who did not.

Researchers are also evaluating more sophisticated radiotherapy approaches that are safer and more effective. As one example, a recent study that compared intensity-modulated radiation therapy (IMRT) with intensity-modulated proton therapy (IMPT) (see **Sidebar 31**, p. 114) for patients with a certain type of head and neck cancer arising in the tonsil or base of tongue found that IMPT was as effective as IMRT at controlling the disease, helped more patients live longer, and caused fewer serious side effects (615). These findings suggest that proton therapy could be considered a new treatment option for this cancer.

Stereotactic body radiotherapy (SBRT) is an advanced approach to radiotherapy that can target radiation to tumors more precisely than traditional radiotherapy. Higher doses and fewer sessions of radiation can be used than with traditional radiotherapy and healthy tissues surrounding a tumor are spared from damage caused by the radiation, which can reduce the long-term adverse effects. Given the potential benefits of SBRT, many clinical trials are testing ways to incorporate these treatments into clinical care, including in the treatment of patients with metastatic cancer. Recent studies have shown that stereotactic radiotherapy targeted to the initial cancer site from which tumors have metastasized can be effective for patients who have metastatic tumors at a limited number of sites, referred to as oligometastatic tumors (616). Similarly, targeting a limited number of metastatic sites that have progressed after systemic therapy with SBRT can be effective as shown in patients with lung cancer (617).

Stereotactic radiotherapy targeted to oligometastatic tumors can reduce the chances of disease progression and increase survival (618-621). In addition, data from a recent clinical trial support the use of stereotactic radiation even among patients with 5 to 20 brain metastases (622). The study showed that among patients with melanoma, lung, breast, and other cancers that had metastasized to the brain, stereotactic radiation

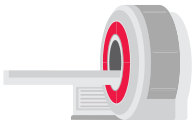
SIDEBAR 31

Using Radiation in Cancer Treatment

Ionizing radiation has two major applications in cancer care. **Radiology** largely uses low-energy radiation to image tissues for diagnosing cancer, whereas **radiotherapy** uses high-energy radiation to treat cancer.

Types of radiotherapy include:

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 (IMRT)**—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 superficial radiation with either electron beam or low energy (kilovoltage) radiation directly on tumors that have been exposed during surgical procedures, and more commonly to the tumor cavity immediately after cancer removal.
- **Stereotactic radiotherapy** delivers radiation to very well-defined smaller tumors, typically using many beams or beamlets 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 (SBRT) (to treat small tumors within the rest of the body).

PARTICLE THERAPY

Delivers radiation doses by protons or carbon ions, instead of X-rays. These heavy charged particles have beneficial physical properties, allowing most of the radiation dose to be deposited in the target, whereas standard X-ray continues to deposit radiation after treating the tumor (known as "exit dose"). By reducing exit dose, particle therapy may reduce normal tissue exposure to radiation. In pediatric, adolescent, and young adult patients, proton therapy can reduce treatment-related side effects while maintaining equivalent tumor control and survival compared to photon radiotherapy. Proton therapy may also be helpful in cases requiring multiple courses of radiation, or in patients with syndromes that increase radiation sensitivity. Although of great interest, proton facilities are more expensive than traditional facilities. The benefit of particle therapy to the broader population of adults with cancer remains to be defined, and is currently being tested in large, randomized trials.

BRACHYTHERAPY

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

RADIOISOTOPE OR RADIONUCLIDE THERAPY

Delivers radiation to the tumors via systemic ingestion or infusion of radioisotopes, usually linked to an antibody or a protein segment (peptide) to direct the radioisotope to tumor cells.

Uses of Radiotherapy

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

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

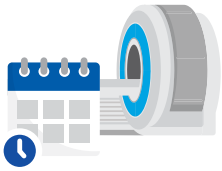
NEOADJUVANT RADIOTHERAPY
Used to shrink a tumor so that it can be subsequently treated by a different method, such as surgery.

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.

reduced symptom burden and improved daily functioning compared to a standard memory-sparing whole-brain radiation therapy. Similar findings from a second clinical trial confirmed that stereotactic radiation is a safe and effective

Many cancer patients in the United States, **especially those from medically underserved populations, miss their recommended radiation appointments**, increasing their risk of recurrence and death.



A national effort led by the American College of Surgeons that **identified the specific reasons patients missed radiation appointments and then implemented tailored, system-level solutions** using educational toolkits, webinars, and peer-learning sessions, reduced the rates of missed radiotherapy appointments across 194 cancer centers by more than 30% helping more patients receive their recommended treatment.

Source: (628). W47

alternative to whole-brain radiation for patients with small cell lung cancer with up to 10 brain metastases, provided they undergo close follow-up monitoring (623).

Another recent advance in radiotherapy is the emergence of hypofractionated radiotherapy, whereby patients receive fewer but higher daily doses of radiotherapy compared to the traditional regimen (624). Patients who receive hypofractionated radiotherapy complete their radiotherapy over a shorter period and in fewer treatment sessions. Research indicates that this approach is just as effective as traditional, longer radiation courses, while also offering benefits like fewer side effects, improved quality of life, and greater convenience for patients (625). A clinical study with 10 years of follow-up demonstrated that hypofractionated radiation therapy delivered in just seven treatments was as safe and effective as the conventional 8-week course for men with intermediate-risk prostate cancer, while requiring substantially fewer treatment visits (626). Another long-term follow-up study showed that hypofractionated radiotherapy delivered in a week (compared to a 3-week schedule) was safe and effective and associated with similar outcomes at 10 years in patients with breast cancer (627).

Applying Precision to Radiation Therapy

One of the most exciting and fastest-growing areas in radiotherapy is the use of radiopharmaceuticals or molecularly targeted radiotherapeutics—radiation-emitting molecules that are linked to targeting molecules, which steer the radiation specifically to cancer cells. A particularly promising innovation is theranostics, which combines diagnostic imaging and molecularly targeted radiotherapy to deliver personalized treatment based on a patient's unique tumor characteristics (see **Sidebar 32**, p. 116). A number of such diagnostic-therapeutic pairs have been approved by FDA in recent years for the management of certain patients with neuroendocrine tumors and prostate cancer (223,629,630), and many more are at various stages of preclinical and clinical testing (631). As of July 2025, more than 400 clinical trials were registered in theranostics and radioligand therapy, evaluating more than 20 distinct molecular targets with additional targets in preclinical development (632,633).

Molecularly targeted radiotherapeutics hold great promise for transforming cancer treatment, although challenges such as regulatory hurdles and complex manufacturing remain to be addressed. Moreover, access to these treatments has mostly been limited to high-income countries, as challenges like limited funding, shortages in sophisticated facilities for delivery, and trained medical personnel continue to hinder broader global use (605). Ongoing research aims to improve tumor targeting while minimizing harm to healthy tissues. Scientists are exploring a range of novel radioisotopes that emit different types of radiation, along with various targeting molecules, such as engineered proteins and antibody derivatives, to enhance radiotherapeutic delivery and reduce toxicity.

Advances in Treatment With Chemotherapy

Chemotherapy, which involves the use of chemicals to kill cancer cells, was first introduced as a pillar of cancer treatment in the early- to mid-20th century (636). Chemotherapy remains a backbone of cancer treatment, and its use is continually evolving to minimize potential harm to patients, while maximizing its benefits.

As with surgery and radiotherapy, chemotherapy is more commonly used to treat cancer in combination with one or more additional types of treatments. Newer and more effective chemotherapeutics continue to be evaluated in clinical research. In addition, researchers are continually investigating optimal dosage and sequence of chemotherapy delivery, new formulations and delivery methods, and novel combinations, particularly with molecularly targeted therapeutics or immunotherapeutics, to improve patient outcomes. As one example, in September 2025, FDA approved the gemcitabine intravesical system (Inlexzo), a device designed to continuously deliver the chemotherapeutic directly into the bladder for weeks at a time, offering a new bladder-preserving treatment option for certain patients with bladder cancer (637).

On the basis of a recent clinical study, patients with advanced NSCLC whose tumors harbor epidermal growth factor receptor (*EGFR*) gene alterations experienced improved overall survival when treated with a combination of chemotherapy

SIDEBAR 32

Advances in Theranostics

Theranostics, also referred to as theragnostics, is a cancer treatment strategy in which cancer is visualized by positron emission tomography/computed tomography (PET/CT) imaging using molecules that are linked to weak radionuclides and bind to specific target proteins on the surface of cancer cells. Once the presence of cancer is confirmed, the same targeting molecules, often labeled with more potent radioactive compounds, are then used to kill cancer cells.

Cancer Type	Diagnostic Agent (to visualize cancer)	Therapeutic Agent (to eradicate cancer)
NEUROENDOCRINE TUMORS	**Gallium Ga 68 dotatate** (Netspot) FDA-approved in 2016	**Lutetium Lu 177 dotatate** (Lutathera) FDA-approved in 2018*
PROSTATE CANCER	**Gallium Ga 68 gozetotide** (Locametz) FDA-approved in 2022	**Lutetium Lu 177 vipivotide tetraxetan** (Pluvicto) FDA-approved in 2022*

* Since the initial approval, FDA has expanded the use of both radiopharmaceuticals to treat patients earlier in the course of the disease.

Ongoing clinical studies are evaluating whether these radiopharmaceuticals, both as single agents and in combination with other therapeutics, can benefit additional patient populations. For example:

- In a clinical trial, lutetium Lu 177 vipivotide tetraxetan delayed cancer progression in patients with oligometastatic prostate cancer who are still responding to antihormone therapy (634). Currently, the therapeutic is approved only for patients who are resistant to antihormone therapy.
- In a separate clinical trial, a combination of lutetium Lu 177 vipivotide tetraxetan and pembrolizumab, a type of immunotherapy, provided durable clinical benefit in a subset of prostate cancer patients (635).

and an EGFR–targeted therapy compared to the EGFR-targeted therapy alone, demonstrating that combining targeted therapeutics with conventional chemotherapies can further extend survival for patients with this common molecular subtype of lung cancer (638). Researchers are also investigating whether, for certain patients, chemotherapies could be replaced with precision medicine approaches that are more effective and less toxic (639). A particularly exciting area in precision oncology is the evaluation of ctDNA as a biomarker to identify cancer patients who can safely forgo chemotherapy as well as to monitor response and resistance to chemotherapy (640-643).

Home-based care has the potential to reduce the burden of frequent treatment visits while expanding access to care for patients who face barriers to reaching cancer centers. In a pilot study, researchers demonstrated that chemotherapy can be safely delivered in patients' homes using virtual monitoring and remote support (644). Home-based chemotherapy was administered without any infusion reactions or treatment-related hospitalizations and was associated with high patient satisfaction.

Treatment with chemotherapeutics can have adverse effects. These can occur during treatment and continue in the long term, or they can appear months or even years later (see **Challenges Faced by Survivors**, p. 145). Researchers are investigating different approaches to make chemotherapeutics safer for patients. A critical area of ongoing research is identifying biomarkers to correctly predict which patients will or will not benefit from chemotherapy, as well as to predict which patients may suffer from chemotherapy-induced toxicities.

Chemotherapeutics such as 5-fluorouracil (5-FU) and capecitabine may cause serious adverse effects. Dihydropyrimidine dehydrogenase (DPD) is a key enzyme that breaks down 5-FU by converting it into an inactive form for elimination from the body. Research has shown that some individuals may carry genetic changes known as DPD deficiency that reduce their ability to safely process this treatment, putting them at higher risk for severe side effects (645,646). To improve patient safety, FDA has recently updated drug labels to include information about this genetic risk, including a boxed warning highlighting the

risk of serious adverse reactions or death in patients with complete DPD deficiency (647). FDA now recommends that clinicians consider testing patients for DPD deficiency before starting treatment.

Advances in Treatment With Molecularly Targeted Therapeutics

Remarkable advances in our understanding of the cellular and molecular alterations that drive tumor growth have ushered in the era of precision medicine, in which patients are increasingly treated with therapies that target the specific molecules and pathways that fuel their cancer progression. As a result, the standard of care is shifting away from a one-size-fits-all approach toward treatments tailored to the patient and the unique characteristics of their cancer (see **Understanding the Path to Cancer Development**, p. 31).

Molecularly targeted therapeutics target tumor cells more precisely than chemotherapeutics, which generally target all rapidly dividing cells. The greater precision of these drugs limits damage to healthy tissues, making them more effective and less toxic than chemotherapeutics (see **Sidebar 33**, p. 118). As a result, molecularly targeted therapeutics are not only saving lives, but also allowing patients with cancer to have an improved quality of life. During the 12 months covered in this report, FDA approved 10 new molecularly targeted therapeutics and expanded the use of two previously approved molecularly targeted therapeutics to treat additional cancer types (see **Table 5**, p. 108). While not covered in this report, FDA also broadened the use of several previously approved therapeutics so they can be used earlier in a patient's treatment journey or for different subtypes of the same cancer.

Diagnostic tests, such as sophisticated DNA sequencing or protein visualizing methods, are commonly used in the clinic to identify molecular changes in patients' cancers, helping to select those who are most likely to benefit from molecularly targeted therapeutics and spare others from unnecessary treatments and side effects. Companion diagnostics are tests that are required for the safe and efficacious use of certain FDA-approved treatments, while complementary diagnostics are tests that are not mandatory but provide additional insights on clinical decision-making. FDA approvals of most new therapeutics are accompanied by the concurrent approval of companion diagnostic tests to facilitate the identification of eligible patients for these treatments.

Unfortunately, because of multilevel barriers to health care, including inadequate health insurance and lack of access to quality cancer care, disparities exist in the utilization of diagnostic testing and molecularly targeted treatments (648,649). As one example, a study using data from the National Institutes of Health (NIH) All of Us Research Program showed that biomarker testing was documented in only 18 percent out of 287 patients with advanced NSCLC, and there were disparities in who received those tests (650). In another study of 1,327 US women with metastatic breast cancer who were treated at academic institutions and who underwent genomic testing between 2015 and 2023, Black patients with alterations in the *PIK3CA* gene were significantly less likely than White patients to receive matched targeted treatment, even though both groups had similar rates of the *PIK3CA* alterations that these drugs are meant to target (648). It is vital that ongoing research and future public health policies are aimed at ensuring equitable access to precision cancer medicine, including tumor genetic testing and the receipt of molecularly targeted therapeutics for all patients.

One of the greatest challenges in cancer treatment is that most cancers eventually become resistant to therapy, limiting the long-term benefit of chemotherapy, molecularly targeted therapy, and immunotherapy. In fact, treatment resistance (see **Sidebar 34**, p. 119) is one of the most elusive questions in cancer science and medicine and contributes to the vast majority of deaths from advanced cancer. Resistance can occur through various mechanisms such as new genetic or epigenetic changes acquired by cancer cells, activation of

The effective use of molecularly targeted therapeutics 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 FDA;
- **Accurately match** patients with a specific therapy;
- **Allow patients to receive 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.

W48

SIDEBAR 33

The Increasing Precision of Molecularly Targeted Therapeutics

Research has increased understanding of the cellular and molecular drivers of cancer. As this knowledge has grown, anticancer therapeutics have become more precisely targeted to those factors, meaning they cause less damage to normal cells. Here, we list the major categories of molecularly targeted therapeutics, grouped by how they work against cancer, with selected examples that have been approved by FDA:

Angiogenesis inhibitors

Block new blood vessel formation, which is vital for tumor growth and metastasis, for example, vascular endothelial growth factor (VEGF) targeted therapeutics, such as bevacizumab (Avastin).

Antibody–drug conjugates

Cause cancer cell death by delivering anticancer drugs specifically to cancer cells, for example, fam-trastuzumab deruxtecan-nxki (Enhertu).

Cell-signaling inhibitors

Block cell-signaling pathways that drive cancer initiation and progression, for example, receptor tyrosine kinase inhibitors, such as the epidermal growth factor receptor (EGFR)–targeted therapeutic osimertinib (Tagrisso) or the cyclin-dependent kinase 4/6 inhibitor ribociclib (Kisqali).

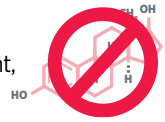
DNA repair inhibitors

Prevent cancer cells from repairing their damaged DNA, causing them to die, for example, poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib (Lynparza).

Epigenome-modifying agents

Block proteins that epigenetically modify DNA, for example, histone deacetylase (HDAC) inhibitors, such as belinostat (Beleodaq).

Hormones/Antihormones



Block hormones such as estrogen or testosterone that drive cancer development, for example, apalutamide (Erleada).

Proteolysis-targeting chimeras (PROTACs)

Mark proteins for destruction, allowing proteasomes, which are part of the normal cellular machinery for breaking down proteins, to break them down, for example, vepdegestrant (Veppanu).

Proteasome inhibitors

Block the action of proteasomes. This may prevent cancer cells from growing and may kill them, for example, bortezomib (Velcade).

Radiation-emitting therapeutics/ Radioconjugates

Deliver high doses of radiation to cancer cells, leading to cancer cell death, for example, lutetium Lu 177 dotatate (Lutathera) or lutetium Lu 177 vipivotide tetraxetan (Pluvicto).

It is important to note that many molecularly targeted therapeutics work by blocking multiple pathways simultaneously. For example, cabozantinib (Cabometyx) inhibits angiogenesis as well as several additional cell-signaling pathways.

alternative growth and survival pathways in cancer cells, treatment-induced damage repair in cancer cells, evasion of cell death by cancer cells, or adaptations through interactions with the surrounding tumor microenvironment (651,652). These diverse and complex mechanisms vary across cancer types and therapies, making resistance difficult to predict and overcome. Advances in genomics, single-cell and spatial technologies, AI, and patient-derived tumor models are providing unprecedented insights into how resistance develops, enabling researchers to identify biomarkers of treatment response, discover new therapeutic targets, and design personalized combination therapies that anticipate and overcome resistance (653).

Highlighted in the following sections are FDA approvals of novel molecularly targeted therapeutics, as well as expanded approvals for previously approved therapeutics to treat new cancer types, that occurred during the 12 months covered in this report.

SIDEBAR 34

The Challenges of Treatment Resistance in the Era of Personalized Medicine

Treatment resistance is one of the key reasons why it is difficult to achieve a cancer cure, even when treatments are initially effective. Research has revealed multiple complex mechanisms by which cancer cells escape and evade treatments. These include mutations in the drug target, use of different signaling pathways that help cancer cells divide rapidly, altered states of cancer cells that help them evade treatment, and cancer cells "hiding" from the immune system. Importantly, genetic mutations in the drug target, although one of the most well-characterized resistance mechanisms, only account for a fraction of treatment failures; many cancers acquire treatment resistance through non-genetic mechanisms.

Because of heterogeneity within a tumor and between tumors, one, more, or all of these mechanisms can coexist in a single patient and confer resistance against treatment. Some cancer cells:

ACQUIRE MUTATIONS in the target of a given treatment that render the therapy ineffective in those cells and their progeny.

Example: Resistance to imatinib in chronic myeloid leukemia.

LEVERAGE REDUNDANCIES among signaling pathways fueling their proliferation to bypass the signaling pathway being targeted with the drug.

Example: Resistance to PI3K inhibitors in ER-positive breast cancer.

EXHIBIT VERY LOW METABOLISM and do not divide. These cells evade treatments that target rapidly dividing cancer cells.

Example: Resistance to chemotherapy.

SWITCH THEIR IDENTITY completely from one type of cell to another such that the pathway being targeted with the drug no longer matters for their survival.

Example: Epithelial-to-mesenchymal transition in multiple cancer types.

REDUCE OR ELIMINATE PROTEINS on their surface that the immunotherapy targets, thus hiding from the immune system. Others can overwhelm the immune cells to such extent that they lose the ability to kill cancer cells.

Example: Resistance to CAR T-cell therapy against the CD19 surface protein in B-cell leukemia.

CAR, chimeric antigen receptor; CD19, cluster of differentiation 19; ER, estrogen receptor; PI3K, phosphoinositide 3-kinase.

Advancing Targeted Approaches in Breast Cancer Care

Thanks to major advances in early detection and treatment, breast cancer death rates have declined significantly in the United States. Just in the past decade, FDA approved nearly 20 new molecularly targeted therapeutics and immunotherapeutics for the treatment of breast cancer. However, breast cancer still ranks as the second leading cause of cancer death in US women (654). Furthermore, breast cancer incidence has been rising over the past two decades, including among women younger than 50 years, and the incidence of metastatic breast cancer has been rising since 2010 (1,655). Therefore, continued innovation and investments in newer and more effective treatments are needed to address the evolving burden of the disease.

For patients with breast cancer, treatment decisions are often guided by the presence or absence of three key biomarkers—estrogen and progesterone hormone receptors (HRs) and the HER2 protein—all of which can drive tumor growth. About 70 percent of breast cancers diagnosed in the United States are characterized as HR-positive/HER2-negative (1). Treatment options for these patients include antihormone therapeutics, also called endocrine therapy, along with another class of molecularly targeted therapeutics known as cyclin-dependent kinase (CDK) 4/6 inhibitors. Endocrine therapy slows or

stops the growth of HR-positive breast cancers in one of three ways: by reducing estrogen levels in the body (e.g., letrozole), blocking estrogen from binding to and activating cancer cells (e.g., tamoxifen), or eliminating the estrogen receptor that drives cancer growth (e.g., fulvestrant).

Unfortunately, most advanced HR-positive breast cancers that initially respond to endocrine therapy eventually progress because they have become treatment resistant (see **Sidebar 34**, p. 119). A common mechanism of acquired resistance to endocrine therapy is the development of activating mutations in the *ESR1* gene, which encodes the estrogen receptor protein, resulting in constitutive (estrogen-independent) activation of the estrogen receptor. Genetic mutations, including those in *ESR1*, occur in approximately 40 percent to 50 percent of patients who receive endocrine therapy and a CDK4/6 inhibitor for metastatic disease (656).

Until recently, fulvestrant was the only FDA-approved endocrine therapy that worked by eliminating the estrogen receptor. However, it must be given by injection, which can be burdensome for some patients, and it also faces the challenge of becoming less effective as tumors acquire *ESR1* mutations (657). These challenges leave patients with limited treatment options and have driven the development of oral drugs that also destroy the mutated estrogen receptor and offer more effective and convenient treatments. In this regard, recent FDA decisions give new hope to certain patients with *ESR1* mutations by providing them with two novel molecularly targeted treatment options with unique mechanisms of action.

In September 2025, FDA approved imlunestrant (Inluriyo) for adults with estrogen receptor–positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer whose disease has progressed following at least one endocrine therapy. FDA also approved the Guardant360 CDx assay as a companion diagnostic test to identify patients with *ESR1* mutations who are eligible for imlunestrant treatment. Imlunestrant is the third FDA-approved drug that works by destroying the estrogen receptor and the second next-generation oral therapy of its kind, offering a new option for patients whose cancers have become resistant to earlier endocrine therapies due to *ESR1* mutations. FDA approval was based on data from a phase III clinical trial in which patients who received imlunestrant lived longer before their cancer worsened compared to those receiving standard endocrine therapy (656). Ongoing research is investigating whether imlunestrant in combination with a CDK4/6 inhibitor can further improve outcomes for patients.

The other molecularly targeted therapeutic approved by FDA, vepdegestrant (Veppanu), belongs to a class of molecules known as proteolysis-targeting chimeras (PROTACs). PROTACs work by inducing targeted degradation of disease-causing proteins. These bifunctional small molecules consist of two protein-binding elements that are attached by a linker; one binds to the protein of interest (target) and the other recruits an E3 ubiquitin ligase, a key component of the cellular protein degradation machinery. By bringing the target close to the E3 ligase, PROTACs initiate breakdown and elimination of the target proteins.

Vepdegestrant is the first PROTAC to be approved by FDA and represents a major breakthrough in drug development. It was approved in May 2026 for adults with estrogen receptor–positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer that has progressed following at least one endocrine therapy. The Guardant360 CDx companion diagnostic test was approved to identify patients with *ESR1* mutations eligible for treatment with vepdegestrant. FDA approval was based on data from a phase III clinical trial demonstrating that among patients with advanced breast cancer whose tumors were estrogen receptor–positive, HER2-negative, and carried *ESR1* mutations, vepdegestrant delayed cancer growth for significantly longer than fulvestrant (658).

One class of molecularly targeted therapeutics that is rapidly emerging as a critical component of breast cancer treatment is antibody–drug conjugates (ADCs), which combine the precision of an antibody that specifically recognizes and binds to a target protein on cancer cells with the cancer-killing power of chemotherapy. Since the first ADC for breast cancer, ado-trastuzumab emtansine (Kadcyla), was approved in 2013, three additional ADCs—fam-trastuzumab deruxtecan-nxki (Enhertu) in 2019, sacituzumab govitecan-hziy (Trodelvy) in 2020, and datopotamab deruxtecan-dlnk (Datroway) in 2025—have expanded treatment options and are now used across multiple breast cancer subtypes, including in patients with advanced disease (659). Research is ongoing to develop more innovative ADCs that can recognize multiple cancer targets simultaneously including novel targets, deliver more sophisticated cancer-killing molecules including immune-stimulating molecules in addition to chemotherapies, and overcome treatment resistance, offering the promise of more effective and personalized therapies for patients with breast cancer (659,660).

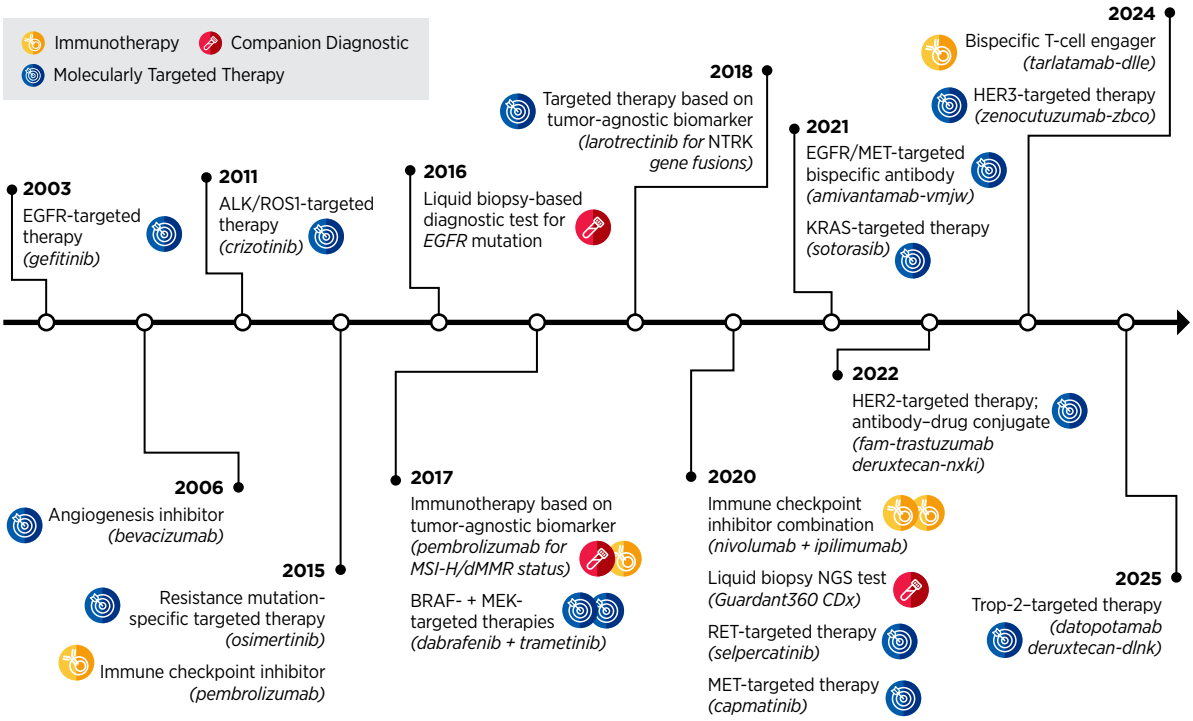
Matching Therapies to the Molecular Drivers of Lung Cancer

Lung cancer is the leading cause of cancer deaths in the United States. An estimated 229,410 new cases will be diagnosed, and 124,990 people will die from the disease in 2026 (2). More than 80 percent of lung cancers diagnosed in the United States are classified as NSCLC. Research over the past several decades has significantly increased our understanding of the genetic drivers of lung cancer, which has led to the development of precision medicine directed at many of these alterations. In fact, lung cancer has served as a model for precision medicine (see **Figure 18**, p. 121). Over the past two decades, successive discoveries of genomic alterations, including in *EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET*, *KRAS*, and *NTRK* genes, and

FIGURE 18

Research Driving Progress Against Lung Cancer

FIRST FDA APPROVALS OF THERAPEUTICS WITH DISTINCT MECHANISMS OF ACTION



Scientific discoveries have identified key genetic changes, such as mutations in *EGFR*, *ALK*, *ROS1*, *KRAS*, among other genes, as well as immune system evasion tactics that drive lung cancer, leading to the development of personalized treatments. These include targeted therapies aimed at the respective proteins and immunotherapies that help the immune system better recognize and attack cancer cells. These advances have dramatically improved outcomes for many patients with lung cancer. Indicated on the timeline are important milestones in lung cancer precision medicine, including the first FDA approvals for molecularly targeted therapeutics or immunotherapeutics that have distinct mechanisms of action.

development of molecularly targeted treatments that block the function of the mutated proteins have transformed treatment from a one-size-fits-all approach to one in which therapy is increasingly guided by the unique molecular features of each patient's tumor. Thanks to these breakthroughs in treatment, as well as improved prevention and earlier detection, the decline in lung cancer death rates has accelerated in the past decade.

Three new molecularly targeted therapeutics approved by FDA during the 12 months covered in this report provide additional treatment options for patients with NSCLC, helping more patients receive therapies tailored to the specific characteristics of their tumors. Two of the new treatments, zongertinib (Hernexeos) and sevabertinib (Hyrnuo), were approved for adults with advanced NSCLC whose tumors have certain mutations in the *HER2* gene. *HER2* mutations are found in approximately 2 percent to 4 percent of NSCLC cases (661). This subtype of NSCLC has a higher incidence of brain metastases than those without *HER2* mutations or with other gene mutations. Although one FDA-approved HER2-targeted therapy was already available for NSCLC patients (223), it may cause serious side effects. Other therapeutic options for these patients include drugs that target multiple related proteins and have limited benefit but substantial toxicities, underscoring the need for more effective and better-tolerated therapies.

In August 2025, FDA approved zongertinib, a new targeted treatment option taken orally, for patients with unresectable or metastatic NSCLC such as **James Gregory (Greg) Cisneros** (see p. 122) whose tumors have *HER2* alterations known as

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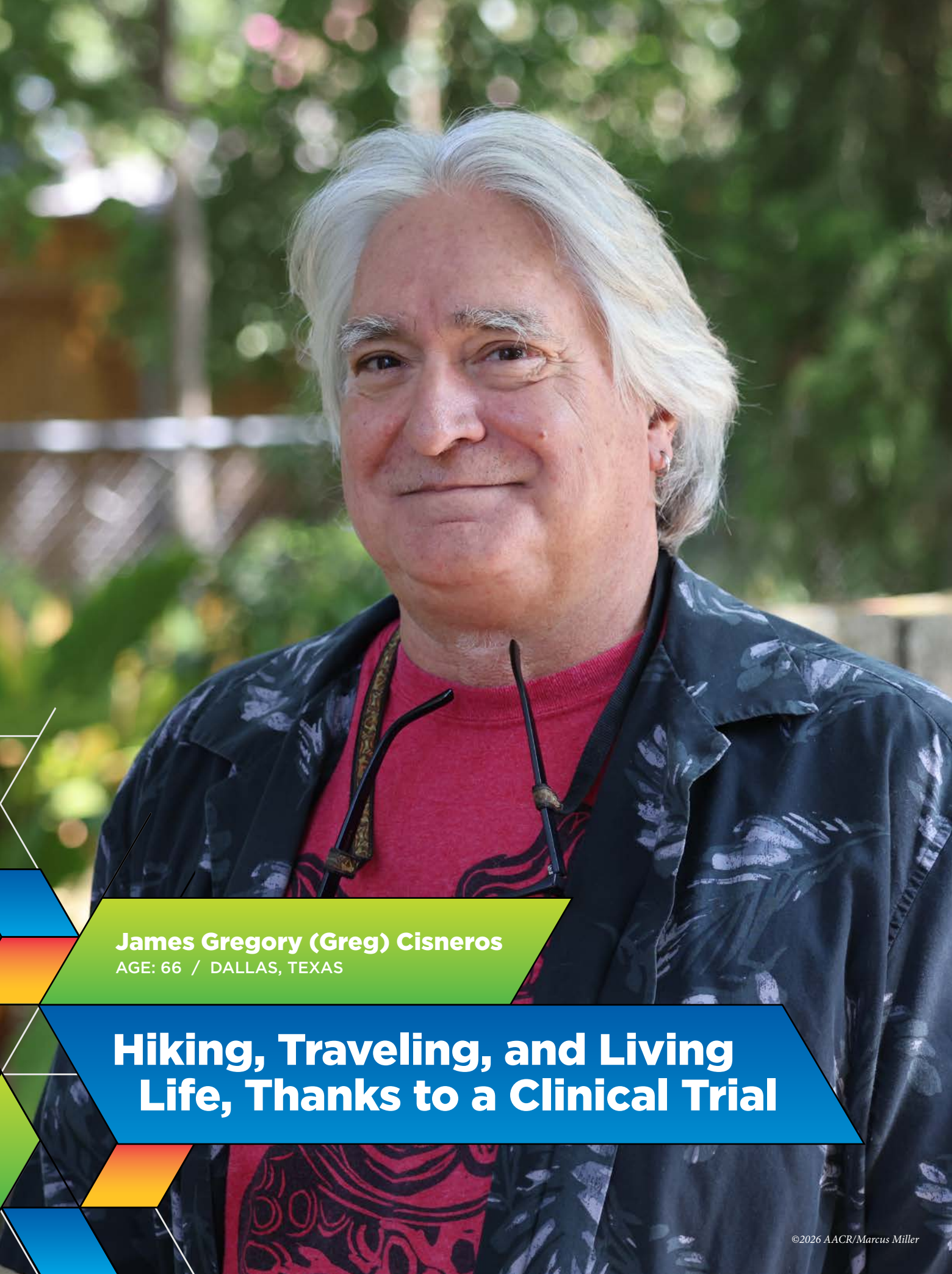

James Gregory (Greg) Cisneros
AGE: 66 / DALLAS, TEXAS

Hiking, Traveling, and Living Life, Thanks to a Clinical Trial

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Adventure has long been part of James Gregory (Greg) Cisneros's life. The 66-year-old retired flight attendant was born in Texas and grew up in Peru. Since retiring, he's devoted his time to traveling, surfing, printmaking, creating music with friends, and hiking and backpacking with his wife, Tina.

During a routine physical examination in June 2020, everything changed for Greg. He casually mentioned to his physician that he had a "spongy" feeling while breathing when he woke up most mornings. The comment prompted a chest X-ray, which revealed a mass in his lower right lung. "I had no idea there was anything wrong," Greg recalled. "In fact, Tina and I had run 5 kilometers the week before, because we were training for a race." Additional testing led to a diagnosis of a rare subtype of non–small cell lung cancer that is more common in people who have never smoked. "When I said I had lung cancer, everybody was like, 'Well, I've never seen you smoking,'" Greg recalled.

In September 2020, Greg had surgery to remove the lower lobe of his right lung. Four months of chemotherapy followed. Treatment was physically taxing. "Imagine the worst hangover you've ever had and multiply it by 2 or 3 and let it last 3 weeks," Greg said. The treatment initially eliminated all signs of disease, but its side effects sometimes left him bedridden for days at a time with severe fatigue and nausea.

Less than a year later, routine follow-up scans revealed that the cancer had returned in both lungs, marking its progression. Greg had stage IV lung cancer. A biopsy of his tumor showed a *HER2* gene mutation, a genetic alteration that can drive cancer growth. This information opened the possibility for a more personalized treatment approach, and Greg began treatment with a therapy designed to deliver chemotherapy directly to HER2-positive cancer cells. However, his cancer continued to progress.

In March 2023, Greg's oncologist, Dr. Kartik Konduri at Texas Oncology, referred him to Sarah Cannon Research Institute (SCRI) at Mary Crowley where he was enrolled in a clinical trial investigating a targeted therapy called zongertinib (Hernexeos), which was designed to block abnormal HER2 signaling. He began taking four pills each day and his response was dramatic. "There was a rapid disappearance of the masses in my lungs," he said. "Now I've been at around a 95 percent reduction. It's been supereffective." Greg encourages other patients to consider enrolling in a trial. "Absolutely do a trial. You have nothing to lose. And look at the result for me: It's great. I have a life," Greg said.

His quality of life also improved dramatically. While zongertinib caused some fatigue, nausea, and digestive side effects, they were manageable and diminished over time. The difference he felt was stark. "Chemo is destroying your body while curing you," he said. "I was recovering all the time. Compared to chemo, zongertinib is like a vacation. I was living again."

More than 3½ years after starting the clinical trial, Greg still gets CT scans every 12 weeks to monitor his cancer. His disease is under control, and he enjoys swimming regularly, hiking and camping with Tina, and visiting his family in Peru.

The experience also left Greg with a deeper appreciation for science. After his diagnosis, he immersed himself in learning about his cancer and the history of cancer research. Understanding his disease has helped him cope with cancer with greater confidence. Greg hopes that future patients will have access not only to new treatments but also to the knowledge behind them.

The experience also strengthened Greg's belief in the importance of medical research and clinical trials. He credits decades of cancer research and clinical trial participation for the extra time he has to do what he loves. In August 2025, zongertinib received FDA approval for adults with non–small cell lung cancer who have a *HER2* mutation, making the treatment available to more patients.

To policymakers, Greg stresses that continued investment in cancer research is essential for helping people live longer, healthier lives. "Cancer research is about life and living," he said. "Funding that research gives people a better quality of life. It gives them more time to be with their families, to do the things they love, and to live."

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

tyrosine kinase domain activating mutations and who have previously received systemic treatment. FDA also approved a companion diagnostic, the Oncomine Dx Target Test to help identify eligible patients. The approval was based on findings from a phase I clinical trial in which zongertinib shrank tumors in more than 70 percent of patients who had received prior chemotherapy but not a HER2-targeted therapy and in more than 40 percent of patients who had also received prior HER2-targeted therapy, with many responses lasting at least 6 months (661,662). On the basis of additional data, FDA expanded the approval in February 2026 to include patients who had not yet received systemic therapy for advanced NSCLC (663,664).

In November 2025, FDA approved another molecularly targeted therapeutic, sevabertinib (Hyrnuo), for adults with locally advanced or metastatic NSCLC whose tumors have *HER2* tyrosine kinase domain activating mutations and who have received prior systemic therapy. The Oncomine Dx Target Test was approved as a companion diagnostic. Sevabertinib is an oral treatment that blocks the activity of altered EGFR and HER2 proteins, both of which can drive the growth of NSCLCs. FDA approval was based on findings from a phase I/II clinical trial in which sevabertinib shrank tumors in more than 70 percent of patients who had received prior chemotherapy but not a HER2-targeted therapy and in nearly 40 percent of patients who had also received prior HER2-targeted therapy, with many responses lasting at least 6 months (665,666).

About 2 percent to 3 percent of patients with NSCLC harbor alterations in the *EGFR* gene known as exon 20 insertion. These patients do not respond well to traditional EGFR-targeted therapeutics, such as osimertinib (Tagrisso), and generally have a poor prognosis (639). While a molecularly targeted treatment regimen comprising the bispecific antibody amivantamab (630) combined with chemotherapy is effective for these patients, it requires intravenous infusions, highlighting the need for more convenient and chemotherapy-free oral treatment options. Sunvozertinib (Zegfrovy) is an oral targeted therapy that works against *EGFR* exon 20 insertion mutations, including many different forms of these mutations. In July 2025, it was approved by FDA for adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease had progressed during or after chemotherapy treatment. FDA also approved the Oncomine Dx Express Test as a companion diagnostic.

FDA's decision was based on the results of a phase II clinical trial in which tumors shrank or disappeared in more than 45 percent of patients who received sunvozertinib (667,668). Emerging data indicate that results with sunvozertinib are superior to those of chemotherapy even for patients who have not received any prior treatments, suggesting potential efficacy of the therapeutic in a broader patient population (639).

Targeting a New Vulnerability in Ovarian Cancer

Ovarian cancer that is resistant to platinum-based chemotherapy is a leading cause of gynecologic cancer–related mortality worldwide (669). Treatment options for these patients are limited and comprise a different class of chemotherapeutic with or without targeted therapeutics, depending on tumor characteristics. Glucocorticoids are a class of hormones that regulate cellular metabolism, immune responses, and stress responses in the body. They work by attaching to proteins called glucocorticoid receptors, which are present in cells throughout the body. Glucocorticoid receptors are also highly expressed in ovarian cancer cells and provide survival signals to these cells, leading to tumor growth and reduced sensitivity to chemotherapy (669).

Relacorilant (Lifyorli) is a novel, the first of its kind, molecularly targeted therapeutic that selectively blocks glucocorticoid receptor function and glucocorticoid-induced survival signals, thereby increasing sensitivity of tumors to chemotherapy. In March 2026, FDA approved relacorilant in combination with chemotherapy for the treatment of adults with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received prior systemic treatment regimens, at least one of which included the molecularly targeted therapeutic bevacizumab. FDA's decision was guided by results from a phase III clinical trial in which patients who received relacorilant along with chemotherapy experienced longer survival compared to those who received chemotherapy alone (669).

Increasing Precision in the Treatment of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men living in the United States (2). In 2026 alone, more than 333,000 men are expected to be newly diagnosed with the disease (see **Table 1**, p. 19). Most prostate cancers are initially driven by male hormones called androgens and respond to treatments that block these hormones, but many eventually become resistant and continue to grow. A signaling pathway that is vital for driving cell multiplication and survival, and involves PI3K, AKT, and PTEN proteins, is overactivated in many cancers, including prostate cancer. Research has shown that inactivation of the *PTEN* gene is associated with faster disease progression and poorer outcomes in patients with advanced prostate cancer that has stopped responding to hormone therapy. One reason why prostate cancers with *PTEN* inactivation are more difficult to treat is that PTEN deficiency leads to the activation of a growth-promoting pathway involving PI3K and AKT, which drive tumor growth. Growing evidence suggests that deficiencies in *PTEN* also drive the progression of advanced prostate cancer that still responds to hormone therapy (670).

Capivasertib (Truqap), first approved by FDA in 2023 for certain breast cancer patients, was the first molecularly targeted therapeutic that works by blocking the function of AKT. In June 2026, FDA expanded the approval of capivasertib for adults with metastatic hormone therapy–sensitive prostate cancer that is PTEN-deficient as detected by an FDA-authorized test. FDA also approved the VENTANA PTEN RxDx Assay as a companion diagnostic text to identify patients with PTEN-deficient prostate cancer eligible for treatment with capivasertib. The approval of capivasertib was based on a phase III clinical trial in which adding capivasertib to standard treatment delayed the growth and spread of PTEN-deficient advanced prostate cancer by more than 7 months compared to standard treatment alone (670).

Personalizing Treatments for Patients With Rare Cancers

Rare cancers are defined by NCI as cancers that occur in fewer than 15 out of 100,000 people each year. Most blood cancers and all childhood cancers are considered rare cancers. Due to their low incidence, rare cancers can be challenging for researchers to study and for physicians to treat (see **Sidebar 35**, p. 128). During the 12 months covered by this report, FDA approved a number of molecularly targeted therapeutics and immunotherapeutics for treating rare cancers, bringing the promise of precision medicine to patients who often have fewer treatment options.

Cholangiocarcinoma, or bile duct cancer, is a rare cancer that grows in the small tubes called bile ducts, which carry bile, a fluid that helps with digestion. According to NCI, in the United States, cholangiocarcinoma affects about 8,000 people per year. Cholangiocarcinomas carrying genetic alterations known as neuregulin 1 (*NRG1*) gene fusion are extremely rare but can be life-threatening.

In less than 1 percent of all solid tumors, structural variations (see **Sidebar 7**, p. 40) in the *NRG1* gene can lead to the formation of NRG1 fusion proteins that contribute to cancer growth. NRG1 fusion proteins activate growth signals in cancer cells by binding to a cell surface protein called HER3, which then pairs with HER2, another cell surface protein involved in cell growth. The formation of the HER2/HER3 complex sets off a signaling cascade that promotes tumor development. As a result, targeting HER2 and HER3 has emerged as a promising treatment strategy for patients with NRG1 fusion–positive cancers, regardless of where the cancer originates in the body. As reported in the *AACR Cancer Progress Report 2025*, zenocutuzumab-zbco (Bizengri) was the first HER3-targeted therapeutic approved by FDA. It was approved for patients with NSCLC or pancreatic cancer harboring an *NRG1* gene fusion (513).

In May 2026, FDA expanded the approval of zenocutuzumab-zbco for treating adults with advanced, unresectable or metastatic cholangiocarcinoma harboring an *NRG1* fusion who experienced disease progression on or after prior systemic therapy. The approval was based on data from a phase II clinical trial in which tumors shrank or disappeared in nearly 37 percent of patients after treatment with zenocutuzumab-zbco (672).

Personalizing Treatments for Pediatric and Young Adult Patients With Rare Brain Tumors

Brain and other nervous system tumors are the second most diagnosed cancer in children. Diffuse midline gliomas (DMGs) are rare, fast-growing, highly aggressive cancers arising in the brain or spinal cord and have a dismal prognosis. Children with diffuse intrinsic pontine glioma (DIPG), a form of DMG, only survive about 12 months after diagnosis (673). Researchers are exploring new and improved therapeutic options for patients with DMG.

DMGs with the H3K27M mutation mostly affect pediatric and young adult patients. The H3K27M mutation is a change in a protein called histone H3, which helps package DNA and control how genes are switched on and off (see **Epigenetic Changes**, p. 44). DMGs with the H3K27M mutation typically occur in critical areas of the brain such as the brainstem or thalamus, where surgery is not possible, and standard treatment with radiation has limited benefits.

Despite many clinical trials, no treatments have improved survival, and most patients live only 11 to 15 months after diagnosis (674). Therefore, FDA approval of dordaviprone (Modeyso) in August 2025 offered new hope for patients facing this devastating disease such as **Benjamin (Ben) Stein-Lobovits** (see p. 126). Dordaviprone works by targeting two important proteins involved in certain brain tumors. First, it blocks dopamine receptors, which are proteins on the surface of brain cells that normally respond to the chemical messenger dopamine in the brain. In some aggressive brain cancers, these receptors are overactive and help tumors grow. Second, dordaviprone activates the protein caseinolytic protease P inside mitochondria, the organelles that provide energy to cells. By activating this protein, dordaviprone disrupts the mitochondrial function, causing stress that leads to cancer cell death. This combined effect helps slow tumor growth.

FDA granted approval to dordaviprone for adults and children age 1 year and older with DMG that has the H3K27M mutation and has worsened after earlier treatment. This is the first approval of a systemic therapy for DMG, marking an important milestone for patients who previously had no effective options. The approval was based on data from five clinical studies

continued on page 128

Benjamin (Ben) Stein-Lobovits
AGE: 40 / BERKELEY, CALIFORNIA

Watching His Daughters Grow Up After a Diffuse Midline Glioma Diagnosis

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In 2017, Benjamin (Ben) Stein-Lobovits, at age 31, had recently gotten married. Ben and his wife bought a house and adopted a dog. They were looking forward to starting a family when he began to experience unusual symptoms.

Ben started having worsening headaches and a feeling of numbness in his tongue. At first, Ben brushed them off. "Then, at work, I turned a corner and just walked into a wall," he recalled. "I said to myself, 'That was very, very weird,' and I knew something was wrong."

Ben's stepfather is a family physician who rarely worries about minor symptoms. When Ben told him about his symptoms, however, his stepfather recommended seeing a neurologist. Although the neurological exam appeared normal, Ben insisted on getting an MRI, which revealed a brainstem glioma—an aggressive brain cancer.

Because of the tumor's location, surgery was not an option and even getting a biopsy was risky. Ben desperately searched for answers about his future. The prognosis was devastating and uncertain. He searched the Internet and found that patients with his disease survived around 10 months. But Ben was determined to beat the odds. "I said to myself, 'That's just a statistic. I'm one of one, and I'm not going to die,'" he recalled.

Before starting chemotherapy, Ben and his wife made the difficult decision to seek out fertility preservation options and freeze his sperm, hoping it would one day allow them to have children. At the time, they had no idea whether that day would ever become a reality.

The months after starting chemotherapy and radiation were difficult. Treatment left him exhausted and depressed, but he remained determined to keep searching for options beyond standard therapy.

Ben immersed himself in scientific literature, leading him to researchers investigating the potential of liquid biopsies—tests that can use blood and other body fluids to reveal molecular features of a tumor. Ben directly reached out to the study's authors and was eventually connected with researchers who tested his cerebrospinal fluid. The test showed that his tumor had an H3K27M mutation, making him eligible for an experimental drug called ONC201. Now known as dordaviprone (Modeyso), the drug targets tumors carrying the H3K27M mutation found in many diffuse midline gliomas.

Even though Ben was eligible to participate in the clinical trial, getting the drug was not straightforward. Through his research and outreach, Ben found physicians willing to enroll him, but he had to travel monthly from California to Washington for treatment. Later, he had to transfer his care to Los Angeles when the original trial site lost funding and closed during the COVID-19 pandemic.

Unlike chemotherapy, the investigational therapy caused virtually no significant side effects. "That was such a relief after going through chemo and radiation," Ben said.

Nearly 9 years after his diagnosis, Ben is still taking dordaviprone. His tumor has shrunk by about 70 percent and many of his neurological symptoms have diminished. His experience reflects how new treatments are beginning to improve outcomes for patients who have historically had very few options. In August 2025, dordaviprone received FDA approval for adult and pediatric patients with diffuse midline glioma who have an H3K27M mutation.

Long-term survivorship has brought new challenges. While Ben has experienced few lasting side effects from dordaviprone, he continues to manage cognitive difficulties caused by earlier radiation treatment. At 32, he also went on long-term disability. "My cancer journey has totally changed my life," he said. "I'm a different person than I used to be, and that's something I'm still dealing with and grappling with. A sense of self, my career, my purpose. Everything was just gone." Yet he has built a life that once seemed beyond reach.

A few years after his diagnosis, Ben and his wife decided to use his frozen sperm to start a family. They now have two daughters, and much of Ben's motivation comes from watching his daughters grow up. "This treatment is hope," he said. "Hope for the future. To be able to be there for my daughters. I dream of being there on their wedding day."

Ben has become a dedicated mentor and advocate for other patients with diffuse midline glioma. He regularly connects with newly diagnosed individuals, helping them navigate a disease he knows all too well. "Mentorship and advocacy are beyond purposeful to me," Ben said. "Just hearing other people's stories gives me hope."

His message to policymakers is simple. "Don't cut funding," he said. "We need the funding to continue research. I'm living proof of what cancer research can do. We need the research to keep people alive."

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

SIDEBAR 35

The Challenges Posed by Rare Cancers

- Rare cancers affect **fewer than 40,000 people per year** in the United States.
- In 2022, rare cancers **accounted for 27 percent of all new cancer cases** and **30 percent of all cancer-related deaths worldwide** (671).
- **All childhood cancers** are considered rare.
- Rare cancers pose **significant challenges to patients, physicians, and researchers**.

According to NCI, these challenges include the following:

FOR PATIENTS

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.

TREATMENT PROXIMITY

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

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.

LACK OF CONSENSUS

It is hard to know what to do when clinicians do not agree on how to treat their cancer.

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.

NCI 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 (MyPART) Network is a group of scientists, patients, family members, advocates, and health care providers working together to find treatments faster for rare cancers in children, teens, and young adults.

showing that about 20 percent of patients responded to the treatment (674,675). Among those who responded, 73 percent experienced benefits lasting at least 6 months, and 27 percent had benefits lasting a year or longer.

Researchers are also examining immunotherapies such as T-cell therapies including chimeric antigen receptor (CAR) T cells (see **Boosting the Cancer-killing Power of Immune Cells**, p. 137) and T cells targeting tumor proteins called tumor-

associated antigens (TAAs) in some children and young adults diagnosed with DIPG (163,676,677). The CAR T cells—which in this case target the tumor-associated GD2 glycolipid (a lipid molecule attached to a carbohydrate molecule) on the surface of DIPG cells—are administered in small doses and infused directly into the brain. Findings from recent studies evaluating GD2–CAR-T cells and T cells targeting the TAAs PRAME, WT1, and Survivin reported positive outcomes including a complete response, reductions in tumor size, and improvements in cancer-related symptoms.

Bringing the Promise of Precision Medicine to 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.

Acute myeloid leukemia (AML) is the second most commonly diagnosed leukemia in the United States, with 22,720 new cases anticipated in 2026 (2). AML has only 33 percent overall 5-year relative survival rate (1). 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.

Structural variations, also known as rearrangements, in the *KMT2A* gene are observed in up to 80 percent of cases of infant acute lymphoblastic leukemia (ALL) and in 5 percent to 15 percent of children and adults with acute leukemia, including cases that originate in myeloid or lymphoid cells, or a mix of both (678). The *KMT2A* gene, formerly known as *MLL1*, encodes the KMT2A protein, which plays a critical role in normal blood cell development by regulating gene expression through epigenetic mechanisms.

KMT2A rearrangements disrupt normal cell development by causing blood cells to revert to an immature state, preventing them from forming functional blood cells. The result is the formation of leukemia cells instead of mature blood cells. This disruptive process is driven by the interaction of KMT2A with another protein called menin (679). Together, menin and KMT2A form a complex that binds to DNA in the cell's nucleus and triggers harmful genetic programs that lead to leukemia. Acute leukemia with *KMT2A* rearrangements is associated with treatment resistance and poor prognosis (680). In addition to *KMT2A* rearrangements, mutations in the *NPM1* gene, which is detected in up to 30 percent of adult AML cases, also depend on menin to promote leukemia development (681,682).

These discoveries led to the development of menin-targeted therapies (683), culminating in the November 2024 FDA approval of revumenib (Revuforj), the first menin inhibitor, for adult and pediatric patients 1 year and older with leukemia (see **Figure 19**, p. 130). In October 2025, FDA expanded the use of revumenib for relapsed or refractory AML with a susceptible *NPM1* mutation. During the 12 months covered by this report, FDA further expanded its armamentarium of AML therapies by approving ziftomenib (Komzifti), a second menin inhibitor, for adults with relapsed or refractory AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.

Like revumenib, ziftomenib works by blocking the interaction between menin and KMT2A. By binding to menin, it prevents the menin–KMT2A complex from attaching to DNA, thereby halting the abnormal genetic programs that fuel leukemia. As a result, leukemia cells either are driven to mature into healthy blood cells or are eliminated. FDA approval in November 2025 was based on a phase II clinical trial in which more than 21 percent of patients experienced complete remission (cancer no longer detectable in the bone marrow, number of healthy blood cells returned to normal levels) or complete remission with partial recovery of their blood counts (cancer no longer detectable in the bone marrow, partial recovery of the number of healthy blood cells) (686). Research is ongoing to evaluate the efficacy of ziftomenib in combination with other molecularly targeted therapeutics or chemotherapeutics (687).

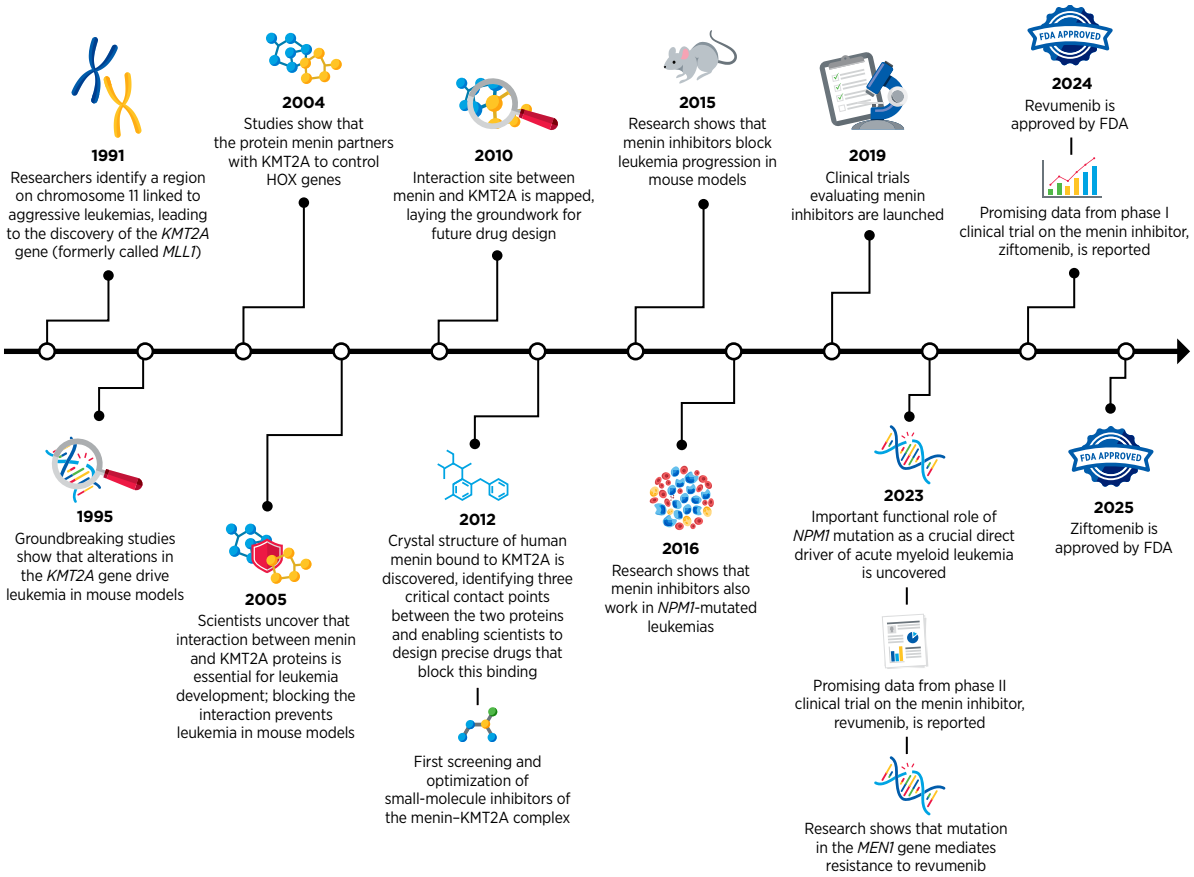
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare type of blood cancer that is highly aggressive. Although many patients respond to treatment with a combination of cytotoxic chemotherapeutics, this treatment strategy ultimately fails to control the disease, leading to poor survival. The protein CD123 is an attractive therapeutic target for BPDCN, given its high level of expression on these cancer cells. In May 2026, FDA approved pivekimab sunirine-pvzy (Decnupaz), a CD123-directed ADC, for adults with BPDCN.

ADCs are a class of molecularly targeted therapeutics that consist of three main components: an antibody that specifically recognizes and binds to a target protein found mostly on the cancer cell surface; a linker that connects the antibody to a chemotherapeutic; and a highly potent chemotherapeutic agent often referred to as a payload. The linker in an ADC is designed to be stable in the bloodstream. Once the ADC attaches to its target on the surface of a cancer cell, it is internalized by the cell. This leads to the cleavage of the linker and the release of the cytotoxic chemotherapeutic from the antibody. Once free, the chemotherapeutic causes cancer cell death. The precision of antibody targeting reduces the side effects of the chemotherapeutic compared to traditional systemic delivery.

Pivekimab sunirine-pvzy is designed to deliver a cancer-killing drug directly to BPDCN cells by targeting CD123 on their surface. FDA approval was based on a phase I/II clinical

FIGURE 19

Milestones in the Development of Menin-targeted Therapy for Leukemia

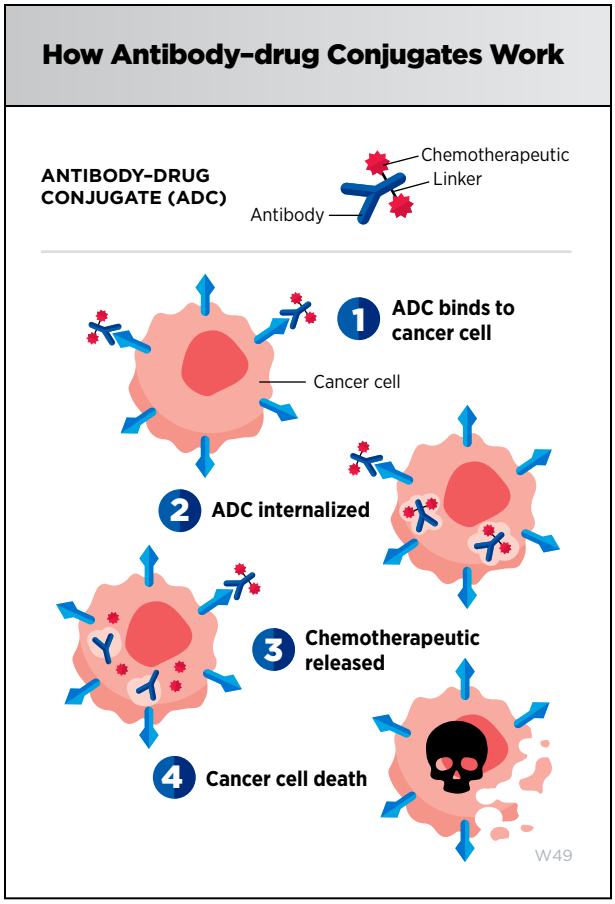


This timeline illustrates key scientific breakthroughs that led to the development and eventual FDA approval of revumenib, a molecularly targeted treatment for aggressive leukemias involving alterations in the *KMT2A* or *NPM1* genes. In 1991 scientists discovered the critical leukemia-linked region on chromosome 11, and in 2004 researchers uncovered how a protein called menin interacts with MLL1, the protein encoded by the *KMT2A* gene, now referred to as KMT2A protein, to drive leukemia growth. Over the next two decades, scientists mapped this interaction, solved its three-dimensional structure, and designed drugs to block it. In 2023, promising clinical trial results showed that the menin inhibitor revumenib could help patients with difficult-to-treat leukemias, leading to its approval by FDA in 2024. In 2025, a second menin inhibitor, ziftomenib, was approved by FDA.

Sources: (512,684,685).

trial in which nearly 70 percent of patients with previously untreated BPDCN who received pivekimab sunirine-pvzy had a complete response (defined as disappearance of disease at each site of initial disease) or a clinical complete response (defined as a complete response with residual skin abnormality not indicative of active disease) (688). Among patients who had received prior therapies, including a previously approved CD123-targeted treatment, tagraxofusp-erzs (Elzonris) (689), nearly 16 percent achieved a complete response or clinical complete response, indicating that pivekimab sunirine-pvzy may be effective even in some patients who have developed resistance to tagraxofusp-erzs and may have limited treatment options.

Non-Hodgkin lymphoma (NHL) is the most common type of blood cancer, with over 80 subtypes. Some common



forms include diffuse large B-cell lymphoma, which is the most aggressive and diagnosed subtype (about 30 percent to 35 percent of NHL cases); follicular lymphoma, which is slow-growing and makes up about 20 percent to 25 percent of NHL cases; and mantle cell lymphoma (MCL), which is relatively less common (about 5 percent to 7 percent of NHL cases) but highly aggressive (513). Over the past decade, an expanding number of molecularly targeted therapies and immunotherapies have become available for patients with NHL, including those with MCL, leading to notable gains in response rates and durability of remission (513).

Despite these advances, MCL often returns after current treatments. Although molecularly targeted therapeutics known as BTK inhibitors have improved outcomes for many patients, treatment options are limited once the disease stops responding to these therapies and if patients are not eligible for immunotherapy. Therefore, FDA approval of sonrotoclax (Beqalzi) in May 2026 for adults with relapsed or refractory MCL who have received at least two lines of systemic therapy, including a BTK inhibitor, offers a new treatment option for these patients.

Sonrotoclax belongs to a class of anticancer therapeutics called BCL-2 inhibitors. BCL-2 is a protein that promotes cell survival by preventing cells from undergoing a natural self-destruction process called apoptosis. Many cancer cells often express elevated levels of BCL-2, and by blocking this protein, sonrotoclax triggers the cells to die by apoptosis. FDA approval was based on phase I/II clinical trial results showing that sonrotoclax reduced or eliminated signs of MCL in more than half of patients who had treatment-resistant disease or relapsed, and these responses lasted a median of nearly 16 months (690).

Sonrotoclax is the second BCL-2 inhibitor approved by FDA. The first in this class, venetoclax (Venclexta), was approved in 2016 for the treatment of certain patients with chronic lymphocytic leukemia. While venetoclax has helped many patients with blood cancers, some eventually become resistant to the drug. Research has shown that sonrotoclax can be effective against cancer cells that had become resistant to venetoclax, including those with a common resistance mutation known as G101V (691).

Advances in Treatment With Immunotherapeutics

The immune system is a complex network of cells (called white blood cells) (see **Sidebar 36**, p. 132), 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 monitors 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 (692). However, as cancer cells acquire new properties during the course of cancer development (see **Understanding the Path to Cancer Development**, p. 31), 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 (693). The field of cancer immunology is focused on better understanding how tumor cells evade the immune system and leveraging this knowledge to develop novel cancer treatments.

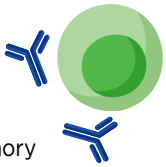
Unprecedented advances in cancer immunology over the past two decades have firmly established immunotherapy as the fifth pillar of cancer medicine (694). Cancer immunotherapy refers to any treatment that works by using the immune system to fight cancer. In various ways the different immunotherapeutics unleash the immune system to fight cancer (see **Sidebar 37**, p. 133).

SIDEBAR 36

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.

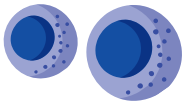
B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help eliminate pathogens as well as help other components of the immune system to function. Some remain as memory B cells to make the same antibody again later, if needed. Understanding of the role of B cells in eliminating 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 several types of T cells:

- **CD4+ T CELLS** help orchestrate the immune response.
- **REGULATORY T CELLS** are a subset of CD+ T cells that keep the immune system from becoming over-active; tumors can exploit these cells to suppress immune attack.
- **CD8+ T CELLS** kill infected, damaged, and abnormal cells, including cancer cells.
- **GAMMA DELTA T CELLS** are rare immune cells that can quickly detect and kill cancer cells; researchers are studying how to use them to develop cancer immunotherapies.

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



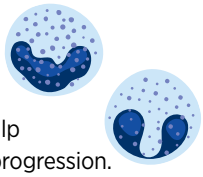
Macrophages eat foreign materials and can ingest and fight against cancer progression, but they can also make molecules that help cancers grow.

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

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.



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 block the checkpoint proteins and can thereby release the brakes on T cells, which trigger previously restrained T cells to attack and destroy cancer cells (695).

The first ICI approved by FDA was ipilimumab (Yervoy) in 2011, which blocks the checkpoint protein CTLA-4 and was authorized for treating metastatic melanoma (see **Figure 20**, p. 134). This was followed in 2014 by the approval of two additional ICIs—nivolumab (Opdivo) and pembrolizumab (Keytruda)—which target a different checkpoint protein, PD-1. These agents work by preventing PD-1 from binding to its partner protein, PD-L1, on cancer cells, thereby lifting the immune system's brakes. Both were also initially approved for metastatic melanoma. In 2016, a fourth ICI, atezolizumab (Tecentriq), which targets PD-L1 directly, was approved for certain types of bladder cancer.

The fourth immune checkpoint protein to be targeted by an FDA-approved therapy is LAG-3. In March 2022, FDA approved relatlimab-rmbw, the first and, so far, only ICI that targets LAG-3, for use in combination with nivolumab (as Opdualag) in patients with metastatic melanoma. While additional ICIs have been approved since then, relatlimab-

SIDEBAR 37

How Immunotherapeutics Work

The way in which different immunotherapeutics unleash a patient's immune system to fight cancer varies:

Some release the brakes on the natural cancer-fighting power of immune cells such as T cells, for example, nivolumab (Opdivo) and pembrolizumab (Keytruda). These therapeutics are commonly known as immune checkpoint inhibitors.

Some amplify the killing power of the immune system by direct infusion of cancer-targeted immune cells called T cells, for example, chimeric antigen receptor (CAR) T-cell therapies such as tisagenlecleucel (Kymriah) or tumor-infiltrating lymphocyte (TIL) therapies such as lifileucel (Amtagvi).

Some increase the killing power of the immune system by enhancing T-cell function, for example, interleukin-2 (Aldesleukin).

Some enhance the cancer-killing power of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).

Some flag cancer cells for destruction by the immune system, for example, bispecific T-cell engagers such as blinatumomab (Blincyto).

Some 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).

rmbw represents the most recent example of an ICI targeting a novel immune checkpoint pathway.

Over the past decade, the use of ICIs has expanded rapidly, and these therapeutics are currently considered among the most exciting approaches to cancer treatment. This is in part because some patients with metastatic cancers who have been treated with these therapeutics have had remarkable and durable responses. For example, long-term results from a clinical trial testing the ICI pembrolizumab in patients with advanced NSCLC showed that 23 percent of patients lived 5 or more years after the treatment, which stands in stark contrast to the historically low 5-year relative survival rate for these patients of just about 5 percent (696).

Another clinical trial that monitored patients with advanced melanoma for at least 7.5 years showed that half of the patients treated with the combination of nivolumab and ipilimumab lived at least 6 years (697). Before ipilimumab was approved in 2011, most patients lived less than a year. Building on these advances, researchers are now studying which ICIs offer the best long-term outcomes and whether single drugs used alone or combinations like nivolumab plus ipilimumab lead to better survival and fewer side effects over time (697,698).

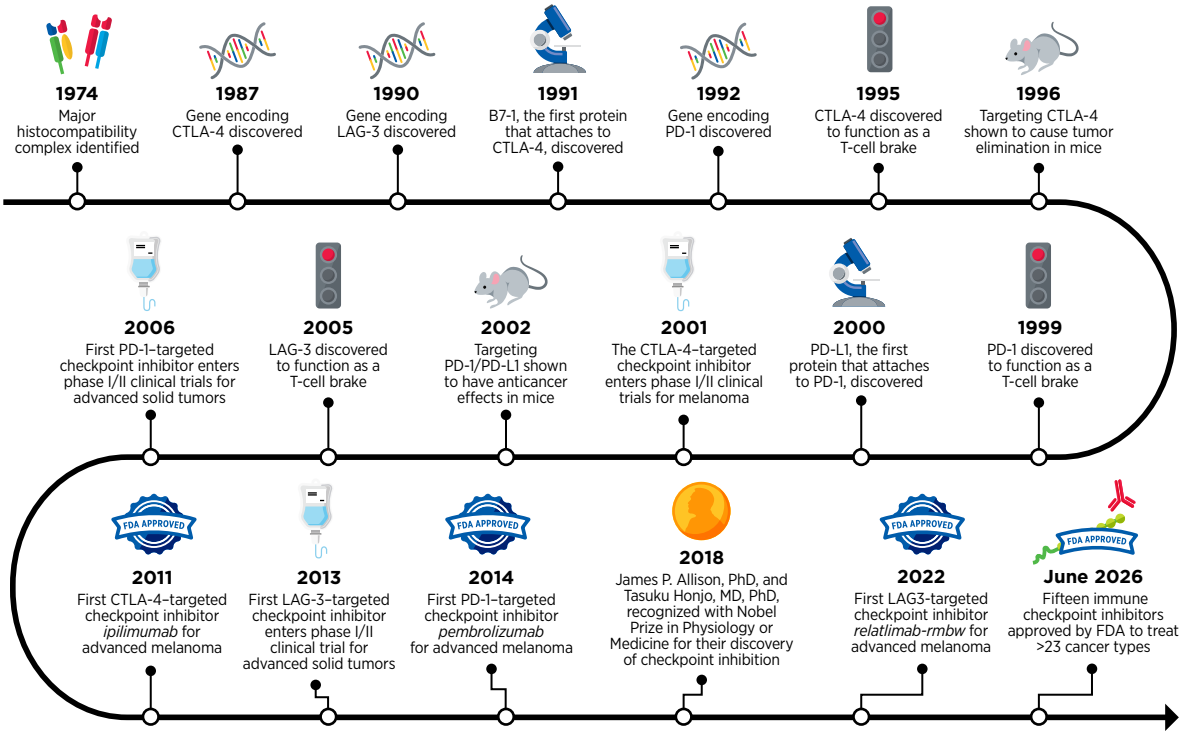
During the 12 months spanning this report, FDA expanded the uses of two previously approved ICIs, durvalumab (Imfinzi) and pembrolizumab (Keytruda), to include additional cancer types. With these latest approvals the total number of ICIs approved by FDA has reached 15 as of June 30, 2026. These groundbreaking treatments are now approved for treating 23 cancer types as well as any type of solid tumor characterized by the presence of certain molecular characteristics (see **Figure 21**, p. 135).

Patients with recurrent ovarian cancer that no longer responds to platinum-based chemotherapy have poor outcomes despite currently available treatments. Although ICIs have transformed the treatment of many advanced cancers, no such therapy had previously been approved for ovarian cancer. This changed in February 2026, when FDA approved pembrolizumab, in combination with chemotherapy with or without the molecularly targeted therapy bevacizumab (Avastin), for patients with PD-L1–positive platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. FDA also approved the PD-L1 IHC 22C3 pharmDx test as a companion diagnostic device to identify patients whose tumors express PD-L1 protein and are eligible for treatment with pembrolizumab. FDA approval was based on data from a phase III clinical trial in which pembrolizumab combined with standard treatment significantly delayed disease progression and improved overall survival (699,700).

In addition to the new approval highlighted above, FDA also expanded the use of pembrolizumab during the reporting

FIGURE 20

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 FDA was ipilimumab, in March 2011. Ipilimumab targets an immune checkpoint protein on T cells, called CTLA-4. 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. Yet another checkpoint protein, called LAG-3, is the target of relatlimab-rmbw, an ICI approved by FDA in March 2022. Decades of basic, translational, and clinical research underpinned the development of these therapeutics, starting with the discoveries of the genes that encode CTLA-4, LAG-3, and PD-1 proteins. Other milestones along the way to FDA approvals include the identification of the brake function of CTLA-4, LAG-3, and PD-1 proteins; the identification of binding partners that attach to and trigger the brake function; and the demonstration that ICIs targeting these brakes can eradicate cancer cells. 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.

period by approving it for earlier lines of therapy and in combination with other treatments for several cancer types. For example, FDA expanded the use of pembrolizumab by approving new combination therapy regimens with molecularly targeted therapeutics that were already individually approved for the same cancer type, including with the ADC sacituzumab govitecan-hziy (Trodelvy) for advanced triple-negative breast cancer and with belzutifan (Welireg) for high-risk kidney cancer.

The second FDA decision that expanded the use of an ICI for a new cancer type was the November 2025 approval of durvalumab with chemotherapy as neoadjuvant and adjuvant treatment, followed by durvalumab alone, for adults with resectable stomach cancer or gastroesophageal junction (GEJ) adenocarcinoma.

Stomach and GEJ cancers are among the leading causes of cancer-related death worldwide. For patients whose cancer can be removed surgically, treatment typically includes

FIGURE 21

Expanding Scope of Immune Checkpoint Inhibitors

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 FDA was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Since then, over the past 15 years, 14 additional ICIs have been approved by FDA.

In addition, FDA has expanded the number of cancer types for which at least one ICI is approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of June 30, 2026, at least one ICI was approved for treating 23 cancer types as well as solid tumors with certain biomarkers. In addition, there are several cancer types for which a deep selection of ICIs is available as a treatment option.

chemotherapy before and after surgery to reduce the risk of the cancer returning. However, many patients still experience disease recurrence. Although several ICIs are already approved for advanced or metastatic stomach and GEJ cancers, treatment options in the earlier, neoadjuvant setting have been limited until the approval of durvalumab. FDA's decision was based on a phase III clinical trial in which patients who received durvalumab with standard chemotherapy before and after surgery were less likely to have their cancer return or worsen, lived longer, and were more likely to have no detectable cancer remaining at the time of surgery than those who received chemotherapy alone (701,702).

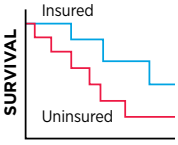
ICIs have yielded extraordinary benefits for many patients. However, they can also have adverse effects, particularly the induction of immune-related adverse events. According to a

new analysis, greater than 56 percent of patients treated with ICIs developed immune-related adverse events within a year, of which nearly 8 percent required hospitalization (703). Patients with comorbidities such as a history of heart attack, heart failure, and kidney disease were at an increased risk. Immune-related adverse events occur because activated immune cells unleashed by ICIs not only attack cancer cells but can also target and injure healthy tissue. To predict which patients are likely to experience serious adverse events and design interventions to combat these events without compromising the anticancer efficacy of ICIs, researchers must better understand why and how adverse events arise (704-706).

One promising approach being evaluated is the use of liquid biopsies (e.g., ctDNA, circulating tumor cells, or circulating proteins in blood) to detect early signs of immune-related tissue damage, which could help identify patients who are developing serious side effects from ICIs before they become clinically apparent (707). Changes in ctDNA concentrations across solid tumors can also predict survival outcomes for patients receiving ICI treatment (708,709). Additionally, researchers have identified a population of tumor-fighting immune cells in the bloodstream that may serve as a blood-based biomarker for predicting which patients are most likely to benefit from ICIs (710). Furthermore, by analyzing thousands of proteins in blood samples from patients with advanced melanoma, researchers have identified potential biomarkers that could help predict response or resistance to immunotherapy and better tailor treatment to individual patients (711).

While ICIs have been transformative for many cancers, only 20 percent of patients respond to these treatments (713). Identifying cellular and molecular biomarkers that can predict whether ICIs are likely to work in a patient is an area of extensive research investigation (714-716). For example, a novel approach that analyzes the spatial organization of tumor and immune cells within the NSCLC tumor microenvironment (see **Understanding the Path to Cancer Development**, p. 31) enabled researchers to make a more accurate prediction of which patients are likely to benefit from ICIs than current biomarkers (715). Another study identified mutations in the *PPP2R1A* gene as a promising biomarker of response to immunotherapy, finding that patients whose tumors carried these mutations lived longer and responded better to treatment across multiple cancer types (716). Biomarkers can also help identify patients unlikely to benefit from ICI therapy, sparing them from unnecessary side effects, high treatment costs, and delays in receiving more effective alternatives.

Immune checkpoint inhibitors (ICIs) have markedly improved survival among patients with metastatic melanoma, lung cancer, and kidney cancer. However, nationwide cancer registry data suggest that the **survival gap between privately insured and uninsured patients with these cancers has widened** since ICIs became available.



Source: (712).

W50

Another important area of scientific inquiry is to identify behavioral and clinical factors, such as diet, physical activity, gut microbiome composition, duration and route of delivery of ICI treatment, 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. Many patients with cancer receive medications to combat concomitant health conditions, some of which may have immunomodulating properties. Understanding the impact of common over-the-counter medications on ICI response and associated immune-related adverse events is an area on ongoing research (717,718). Interestingly, recent studies have found that COVID-19 mRNA vaccination may enhance the effectiveness of immune checkpoint inhibitors by stimulating antitumor immune responses, resulting in improved survival among patients with several types of cancer (719,720). However, more recent analyses suggest that the apparent survival benefit may be due to differences in the health and health care between vaccinated and unvaccinated patients rather than the vaccine itself, underscoring the need for further research to determine whether COVID-19 vaccination truly improves ICI effectiveness (721).

Increasing evidence is showing that the gut microbiome—bacteria, viruses, and all other microorganisms that live in the digestive system (see **Microbiome**, p. 48)—can impact response as well as adverse events related to ICIs (722,723). Researchers are examining how the microbiome enhances the effectiveness of ICIs and are exploring strategies to either mimic these effects through therapies or by modifying the microbiome using probiotics, antibiotics, or fecal transplants. In this regard, three recent clinical studies demonstrated that fecal microbiome transplantation can enhance the response to ICIs among patients with lung cancer, kidney cancer, and melanoma who were receiving these immunotherapeutics as single agents or in combination as their initial treatments (724). The data indicated that the benefits of fecal transplant were driven primarily by depletion of harmful microorganisms and the remodeling of the recipient microbial ecosystem. Another study demonstrated that exercise may improve responses to ICIs by altering the gut microbiome and increasing production of microbial metabolites that stimulate antitumor immune cells (725).

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, often the numbers of cancer-killing T cells are insufficient, 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 (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 (726). While many of the ACTs currently in late-stage clinical development, and all that are approved by FDA, utilize patient-derived T cells, ongoing research is looking to harness the cancer-killing power of other types of immune cells, including natural killer (NK) cells and macrophages (see **Sidebar 38**, p. 138).

CAR T-cell therapy is one type of ACT that has generated enormous excitement in recent years. 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. It works by collecting a patient's own immune cells (T cells) and genetically modifying them to produce a special receptor, called a CAR, on their surface. This receptor enables the T cells to recognize and attack cancer cells. After being multiplied into millions in the laboratory, these engineered cells are infused back into the patient to target and destroy the cancer.

Treatment with CAR T cells has demonstrated unprecedented efficacy in certain patients with very advanced leukemia, lymphoma, and multiple myeloma. As of June 30, 2026, seven CAR T-cell therapies have been approved by FDA for treating a range of blood cancers (see **Sidebar 39**, p. 139). During the 12 months covered in the report, FDA expanded the use of lisocabtagene maraleucel (Breyanzi) for adults with relapsed or refractory marginal zone lymphoma who have received at least two prior lines of systemic therapy.

Marginal zone lymphomas are the third most common type of NHL arising from B cells, after diffuse large B-cell lymphoma and follicular lymphoma. Effective treatments that result in deep and long-term responses for relapsed or refractory marginal zone lymphoma are lacking, making the approval of lisocabtagene maraleucel a major advance against the disease. FDA approval in December 2025 was based on a phase II clinical trial in which more than 80 percent of patients responded to the CAR T-cell therapy, with more than half of patients showing no detectable signs of disease after treatment (727,728).

CAR T-cell therapies can cause significant side effects, some of which, such as cytokine release syndrome, a condition characterized by excessive immune activation leading to organ toxicity, and immune effector cell–associated neurotoxicity syndrome, a neurologic condition leading to confusion, speech difficulties, and seizures, can be life-threatening. As more CAR T-cell therapies are approved for additional cancer types, researchers are identifying previously unrecognized toxicities beyond the well-known early side effects, highlighting the need for long-term monitoring and improved strategies to prevent and manage these complications (730). One area of investigation is to identify biomarkers that can predict response to CAR T cells as well as potential side effects (731,732). Other strategies being explored include the development of therapeutic interventions to manage adverse effects and engineering next-generation CAR T cells, such as those with safety switches that can be turned off in real time to fine-tune CAR T-cell activation and reduce toxicity (732,733).

Efforts are also underway to develop CAR T-cell therapies against solid tumors, but several challenges must be overcome. These challenges include identifying tumor-specific cell surface proteins that are present in the tumor but absent in healthy tissue, infiltration of CAR T cells to the inside of solid tumors, and the immunosuppressive nature of the tumor microenvironment. Advances in tissue bioengineering, cell biology, and microfluidics are allowing researchers to develop innovative models that closely mimic human tumors, providing a new tool to evaluate and optimize CAR T-cell therapies for solid cancers (734). Emerging data are showing efficacy of CAR T-cell therapy in a number of solid tumors, including brain cancers, gastrointestinal cancers, and advanced neuroblastoma (735). In addition, researchers are exploring whether other types of engineered immune cells, such as CAR NK cells or CAR macrophages, can effectively treat solid tumors (736,737).

Developing simpler, safer, and faster ways to bring the promise of CAR T-cell therapies to more patients with different types of

In June 2026, the **world's first CAR T-cell therapy for solid tumors was approved** by the National Medical Products Administration in China. The treatment, satricabtagene autoleucel, was **approved for patients with stomach cancer or gastroesophageal junction adenocarcinoma** whose tumors express certain biomarkers and who have failed at least two prior lines of therapy. W51

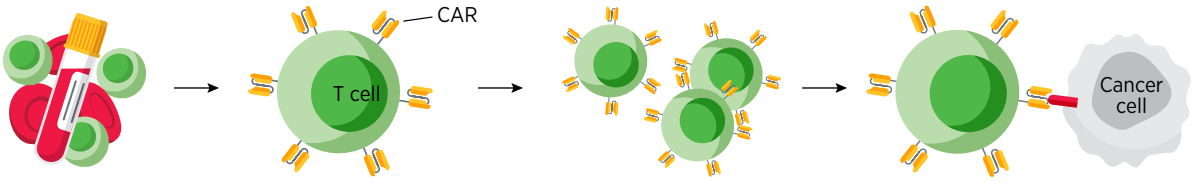
SIDEBAR 38

T-cell–based Adoptive Cell Therapy

Adoptive T-cell therapy, also called cellular immunotherapy, is a direct infusion of cancer-killing immune T cells, thus dramatically increasing the number of immune cells aiming 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. As of June 30, 2026, FDA has approved nine adoptive T-cell therapies.

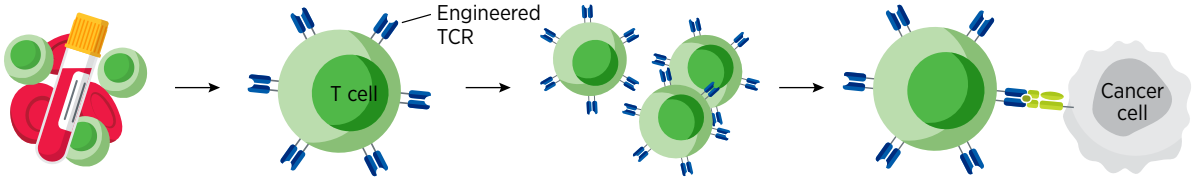
There are three main types of adoptive T-cell therapy:

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY



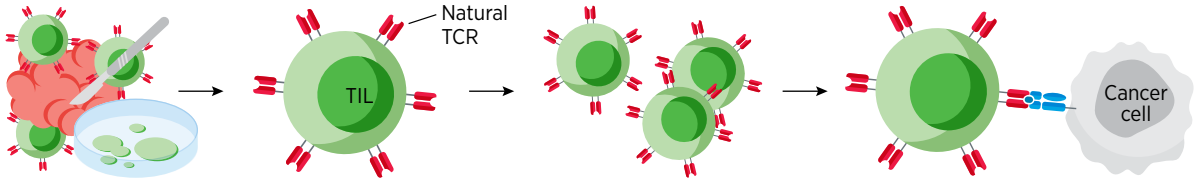
T cells are harvested from a patient's blood and genetically modified in the laboratory so that they have a synthetic protein called a CAR on their surface that recognizes and binds to a specific protein on the surface of the patient's cancer cells. The genetically modified T cells are expanded in number and infused back into the patient. CAR modification helps the T cells directly bind to and eradicate the patient's cancer cells. As of June 30, 2026, FDA has approved seven CAR T-cell therapies for patients with several blood cancer types.

T-CELL RECEPTOR (TCR) T-CELL THERAPY



T cells are harvested from a patient's blood and are genetically modified in the laboratory to carry a new T-cell receptor that enables them to recognize certain protein fragments in 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. As of June 30, 2026, FDA has approved one TCR T-cell therapy, afamitresgene autoleucel (Tecelra), for patients with advanced synovial sarcoma.

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. As of June 30, 2026, FDA has approved one TIL therapy, lifileucel (Amtagvi), for patients with advanced melanoma.

SIDEBAR 39

CAR T-cell Therapies Approved by FDA

As of June 30, 2026, FDA has approved seven distinct chimeric antigen receptor (CAR) T-cell therapies to treat different blood cancers:

Approval Year	Therapy Name	Treatment For
2024	Obecabtagene autoleucel (Aucatzyl)	Adult patients with relapsed or refractory **B-cell precursor acute lymphoblastic leukemia**.
2022	Ciltacabtagene autoleucel (Carvykti)	Adult patients with relapsed or refractory **multiple myeloma**.
2021	Idecabtagene vicleucel (Abecma)	Adult patients with relapsed or refractory **multiple myeloma**.
	Lisocabtagene maraleucel (Breyanzi)	Adult patients with relapsed or refractory **large B-cell lymphoma**. Approved subsequently for adult patients with relapsed or refractory **chronic lymphocytic leukemia** or **small lymphocytic lymphoma**, **follicular lymphoma**, **mantle cell lymphoma**, and **marginal zone lymphoma**.
2020	Brexucabtagene autoleucel (Tecartus)	Adult patients with relapsed or refractory **mantle cell lymphoma**. Approved subsequently for adult patients with relapsed or refractory **B-cell precursor acute lymphoblastic leukemia**.
2017	Axicabtagene ciloleucel (Yescarta)	Adult patients with relapsed or refractory **large B-cell lymphoma**. Approved subsequently for adult patients with relapsed or refractory **follicular lymphoma**.
	Tisagenlecleucel (Kymriah)	Pediatric and young adult patients up to age 25 with **relapsed or refractory B-cell precursor acute lymphoblastic leukemia**. Approved subsequently for adult patients with **relapsed or refractory follicular lymphoma** and **large B-cell lymphoma**.

Source: (729).

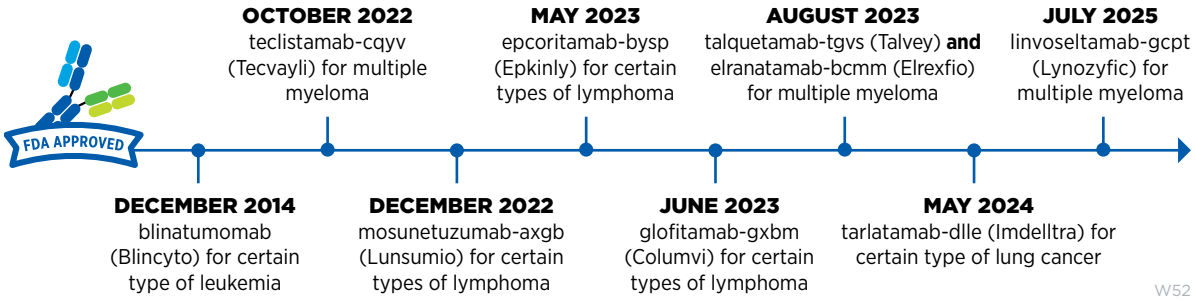
cancer is an area of active research. One area of focus is using T cells collected from healthy donors instead of patients so that these "off-the-shelf" CAR T cells could be readily available for use rather than manufactured for each patient. Additionally, researchers are also investigating new approaches to overcome the financial, manufacturing, and regulatory barriers that currently limit patient access to these potentially lifesaving therapies (738).

Directing the Immune System to Cancer Cells

An immune cell must find a cancer cell before it can attack and eliminate it. Many therapeutics approved by FDA for treating cancer work, at least in part, by helping immune cells find cancer cells. Bispecific T-cell engagers (BiTEs) are one such class of therapeutic antibodies that are moving rapidly from the laboratory to clinical practice. Using two or more arms that are engineered into these antibody molecules, these immunotherapeutics bind to T cells and cancer cells simultaneously. By acting as a connector, BiTEs bring cancer cells in close proximity to the immune 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 ALL called B-cell ALL (739). Unprecedented advances in genetic engineering, molecular biology, and immunology over the past decade have led to

As of June 30, 2026, **FDA has approved nine bispecific T-cell engagers** for the treatment of cancer. Some of these therapeutics have received expanded approvals for the treatment of additional cancers since their first approval.



rapid growth in this innovative new area of cancer medicine. As of June 30, 2026, FDA has approved nine BiTEs for the treatment of cancer, including the most recent approval of linvoseltamab-gcpt (Lynozyfic) that occurred during the 12 months covered in this report (740). Many of these groundbreaking therapeutics are approved for patients with advanced cancer that has returned following several prior treatments or is resistant to therapy.

Multiple myeloma is one of the most common blood cancers in the United States. An estimated 36,000 new cases are expected to be diagnosed in 2026 and more than 10,000 people will succumb to the disease (see **Table 1**, p. 19). The burden is disproportionally higher in the Black population (1). FDA approval of new therapeutics—including proteasome inhibitors like bortezomib (Velcade) and carfilzomib (Kyprolis), immunomodulatory agents like lenalidomide (Revlimid) and pomalidomide (Pomalyst), and immunotherapeutics like the CD38-targeted daratumumab (Darzalex)—have improved outcomes for patients. Despite these advances, many patients whose disease initially responds to the new therapeutics eventually experience relapse owing to treatment resistance.

In July 2025, FDA approved the BiTE linvoseltamab-gcpt (Lynozyfic) for adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Linvoseltamab-gcpt attaches to a molecule called CD3 on T cells with one arm. With the second arm, it attaches to a protein called B-cell maturation antigen, which is present at high levels on the surface of most multiple myeloma cells. By attaching to these molecules on T cells and myeloma cells, the BiTE 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 approval was based on a phase I/II clinical trial in which 70 percent of patients responded to the treatment (741,742). Patients received increasing doses of linvoseltamab-gcpt. This approach, known as step-up dosing, is used in the treatment with BiTEs whereby the dose administered to a patient is raised incrementally before reaching the target dose level. This helps the body's immune system to be primed gradually, thereby reducing the risk of severe immune-related adverse events.

Like ICIs and CAR T cells, BiTEs may cause serious adverse side effects, some of which could be life-threatening if not managed immediately and appropriately by trained medical professionals. While ongoing research is needed to identify ways to minimize the adverse effects, BiTEs are now offering new hope to many patients with advanced cancer who previously were without options and urgently needed effective treatments for their rapidly progressing disease.

Researchers are currently investigating additional approaches to enhance the efficacy of BiTEs and evaluating multispecific (e.g., trispecific and tetraspecific) immune cell engagers designed to direct different types of immune cells, such as NK cells or macrophages, in addition to T cells, toward attacking cancer. Preclinical studies have shown that these innovative approaches can improve immune cell infiltration within tumors, enhance antitumor responses, and when used in combinations may overcome resistance to single-agent therapies, offering hope for more durable and effective cancer treatments (743).

Intercepting the Progression to Blood Cancer Development

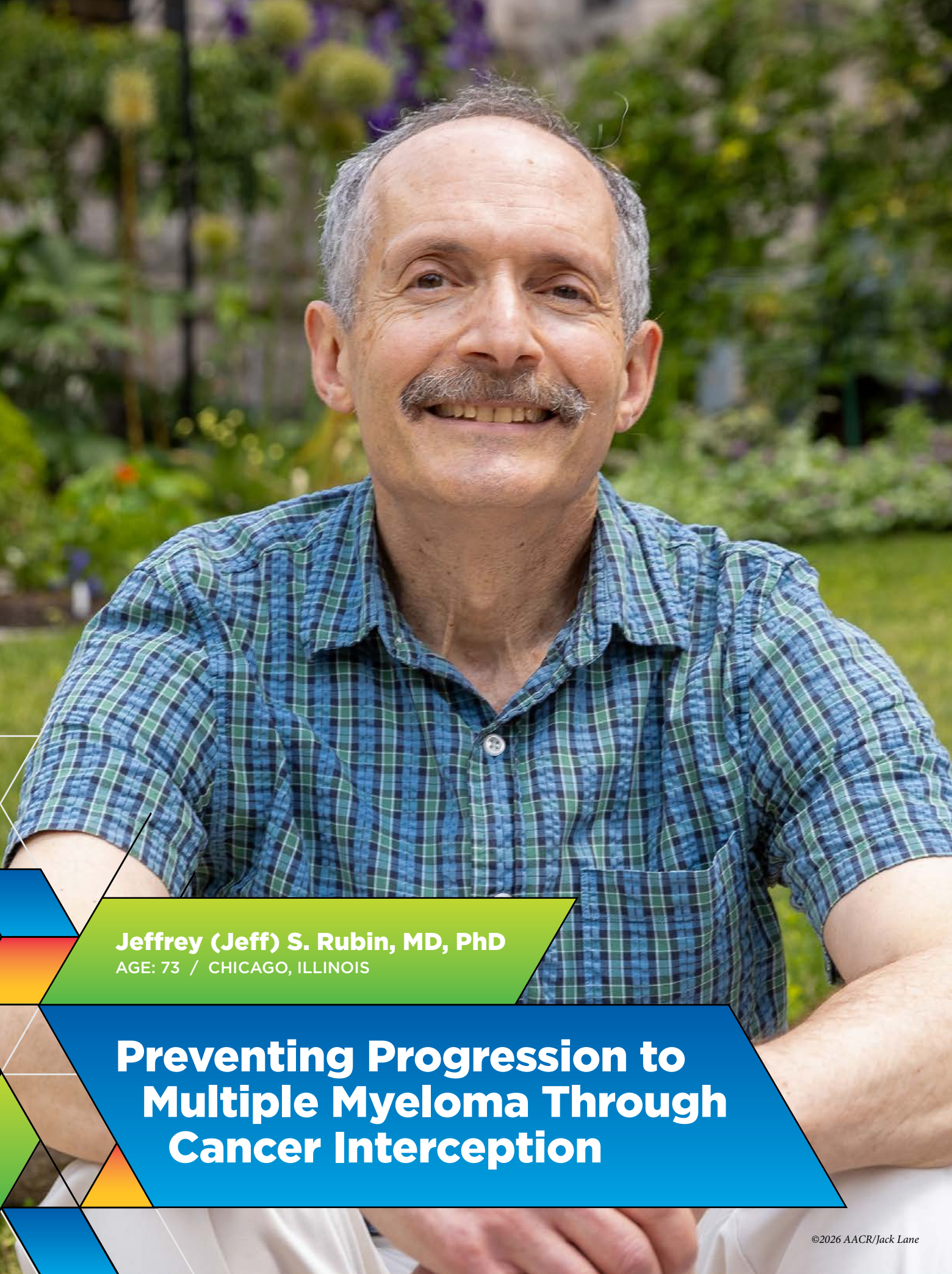
Another group of therapeutic antibodies that mark cancer cells for elimination by the immune system uses a natural process called antibody-dependent cellular cytotoxicity. When the immune system detects a pathogen or damaged cells, B cells produce antibodies that flag unwanted cells or organisms, which are then recognized and killed by immune cells such as NK cells (see **Sidebar 36**, p. 132). 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 and hematologic cancers such as multiple myeloma. Multiple myeloma is a cancer of plasma cells, which are responsible for producing antibodies. In this disease, cancerous plasma cells crowd out the bone marrow and release abnormal antibodies that can damage the kidneys, weaken bones, and cause anemia and high calcium levels. Multiple myeloma often begins silently as a condition called monoclonal gammopathy of undetermined significance (MGUS) and sometimes progresses through an intermediate stage known as smoldering multiple myeloma (SMM) (744-747). Multiple clinical trials are evaluating therapeutics that can intercept MGUS and SMM before they progress into multiple myeloma (513).

In November 2025, FDA approved daratumumab (Darzalex), an established treatment for multiple myeloma, as the first treatment for patients with high-risk SMM such as **Jeffrey (Jeff) S. Rubin, MD, PhD** (see p. 142), offering the potential to intercept progression to active multiple myeloma. The approval was based on a phase III clinical trial in which daratumumab reduced the risk of developing active multiple myeloma or dying by 51 percent compared to active monitoring in patients with high-risk SMM (748).

Daratumumab works by attaching to a protein called CD38, which is found at high levels on the surface of abnormal plasma cells. This attachment has several effects on the cells, most notably flagging them for immune cells, which, upon attaching to another part of daratumumab, are triggered to destroy the abnormal plasma cells. By eliminating or greatly reducing these abnormal plasma cells before they evolve into active multiple myeloma, daratumumab can delay or, in some patients, potentially prevent cancer development.



Jeffrey (Jeff) S. Rubin, MD, PhD
AGE: 73 / CHICAGO, ILLINOIS

Preventing Progression to Multiple Myeloma Through Cancer Interception

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Dr. Jeffrey (Jeff) S. Rubin dedicated his decades-long scientific career at the National Cancer Institute (NCI) to advancing medical research. Jeff, a prostate cancer survivor, also has a strong family history of cancer: His father had multiple myeloma, prostate cancer, and thyroid cancer; his mother had Waldenström macroglobulinemia, a rare blood cancer that shares certain features with multiple myeloma; and several other close relatives have been diagnosed with cancer.

Learning about Jeff's family history of cancer during an annual physical examination, his doctor ordered a blood test that can detect abnormal proteins associated with multiple myeloma. Although the rest of Jeff's bloodwork was normal, the test showed two abnormal protein markers that prompted further evaluation, including bone marrow biopsy and advanced genetic testing. In December 2022, Jeff was diagnosed with high-risk smoldering multiple myeloma (HR SMM).

HR SMM is a precursor of multiple myeloma that may not cause any symptoms but carries a high risk of progressing to active disease. Jeff's test results were concerning because his abnormal plasma cells carried several genetic abnormalities associated with aggressive multiple myeloma. "My oncologist could not offer any treatment because the standard of care at the time was just surveillance," Jeff recalled. "But he told me I should look for a clinical trial because my prognosis would be poor if or when the disease progressed."

Jeff's knowledge of medical science gave him confidence that research was changing the treatment landscape for HR SMM. "What made a difference was knowing I could have options," he said. "I needed to be proactive to find out what would be available and go for it." He contacted former colleagues at NCI and learned about a newly opened clinical trial for patients with HR SMM. In April 2023, just a few months after his diagnosis, he enrolled in the trial.

The clinical trial reflected an emerging concept in cancer care known as cancer interception. Instead of waiting for abnormal plasma cells to progress to active multiple myeloma, researchers were testing whether treating patients earlier could delay or even prevent that progression. "In this sort of trial, there is often not an expectation of a cure. The idea is to minimize disease and continue to monitor it as appropriate," Jeff said.

Participants in the study received an established multiple myeloma treatment regimen consisting of 3 drugs (daratumumab, carfilzomib, and dexamethasone) given for 8 cycles, followed by treatment with daratumumab (Darzalex) alone to keep the disease in check, also called maintenance therapy. Over the course of treatment, Jeff's abnormal blood proteins steadily declined, and testing after completion of the 3-drug treatment phase showed no evidence of measurable residual disease, which means that abnormal plasma cells could no longer be detected with available tests. After 2 years of maintenance therapy, only a very small number of multiple myeloma cells were detectable in Jeff's bone marrow, and the abnormal proteins were still absent from his blood.

Jeff says he tolerated treatment well. Despite experiencing mild fatigue following some of the early treatments, he was able to maintain his healthy routines of jogging multiple times each week and hiking with his wife. He also made time for family and friends.

Receiving treatment at the same institution where he had spent much of his professional life made the experience especially meaningful. During his career helping advance research, Jeff saw firsthand how clinical trial volunteers contributed to medical progress; now he was one of them, and he viewed the study as an opportunity to give something back.

Jeff and his wife have now moved to Chicago to be closer to their daughter, son-in-law, and three young grandchildren. He continues to enjoy jogging, hiking, and nature photography. He also follows the progress of cancer research as a scientist and as someone whose own life has been shaped by it.

In November 2025, daratumumab was approved specifically for patients with HR SMM, the first FDA-approved treatment for this early stage of the disease, giving physicians the ability to intervene before progression to active multiple myeloma. More research is still needed to determine which patients are most likely to benefit from early treatment, but the approval is a major milestone in the growing field of cancer interception.

"We've made quite a bit of progress in my lifetime in reducing death from cancer. I'm glad that there's now an FDA-approved treatment for HR SMM, but more work needs to be done. It's really a partnership of the government and the companies that invest in treatments based on the research that academic scientists have done."

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

Advancing Cancer Survivorship Care

IN THIS SECTION, YOU WILL LEARN:

- As of January 1, 2025, an estimated 18.6 million people were living with a history of a cancer diagnosis in the United States.
- Cancer survivors face a multitude of physical, emotional, and financial challenges because of their cancer and treatment.
- Eating a healthy diet, eliminating alcohol and tobacco use, and engaging in regular physical activity can improve overall health and quality of life during survivorship.
- Childhood, adolescent and young adult, and older adult survivors have unique survivorship needs that require specialized approaches to care.
- Effective survivorship care requires coordinated approaches that help survivors access the care and resources needed to support their long-term health, well-being, and quality of life.
- Caregivers play an essential role in supporting people with cancer, yet they often experience significant challenges of their own. Recognizing and addressing caregiver needs is an important component of comprehensive survivorship care.

According to the National Cancer Institute (NCI), an individual is considered a cancer survivor from the time of diagnosis throughout the remainder of life (749). Cancer survivors represent a diverse population with a wide range of experiences, disease trajectories, and care needs. For example, some individuals complete treatment and remain cancer-free, whereas others may live with cancer as a chronic disease.

Remarkable advances in cancer research and treatment over the past decade have led to more patients living longer and fuller lives after a cancer diagnosis. As of January 1, 2025, more than 18.6 million adults and children with a history of cancer were living in the United States (US), and this number is projected to exceed 22 million by 2035 (13). This represents a substantial increase since 1971, when there were an estimated three million cancer survivors in the United States (750).

AS OF JANUARY 1, 2022
AN ESTIMATED 5 MILLION INDIVIDUALS
IN THE UNITED STATES WERE LIVING WITH
A HISTORY OF A RARE CANCER DIAGNOSIS,
REPRESENTING
NEARLY 28% OF ALL CANCER SURVIVORS

Source: (751). W53

As more people are living longer and fuller lives after a cancer diagnosis, a greater understanding of survivorship experiences is needed. These include physical, psychosocial, and financial challenges that can affect health and quality of life during and after treatment. Many survivors also experience long-term health problems as a result of their cancer and its treatment, known as late effects. These late effects can emerge or persist long after treatment ends, highlighting the importance of long-term follow-up care.

A diagnosis of cancer also impacts friends, family members, and other caregivers, who often serve as the primary support network of the survivor. Survivors and caregivers from medically underserved populations frequently face additional financial, emotional, and logistical burdens that can compound the challenges of survivorship. As a result, survivorship research, support, and care must extend beyond the cancer patient and survivor to include individuals who make up the broader support network.

The following sections highlight key challenges faced by cancer survivors and their support networks, strategies to improve long-term health and quality of life, and evidence-based approaches for delivering high-quality survivorship care.

Challenges Faced by Survivors

Depending on the cancer type and stage, as well as the age at diagnosis, survivorship encompasses a broad range of experiences related to living with and beyond cancer (see **Sidebar 40**, p. 146). Cancer survivors often face physical, psychosocial, and financial challenges that arise from the cancer itself and its treatment. These challenges can emerge during treatment or long after its completion, requiring ongoing care and support.

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 regimen. As cancer survivors are living longer because of better therapies, the development of long-term side effects, such as heart damage (cardiotoxicity), lung damage, loss of bone density, neuropathy, and cognitive decline, is becoming more common and demands a greater understanding to reduce or manage these conditions.

Many common cancer therapies can adversely affect the cardiovascular system, contributing to long-term morbidity and mortality among cancer survivors (752,753). This treatment-related heart damage, known as cardiotoxicity, can occur during or after cancer therapy. Certain chemotherapeutic agents (e.g., anthracyclines), molecularly targeted therapies, and radiation exposure can cause cardiotoxicity, leading to cardiomyopathy, coronary artery disease, heart failure, and other cardiovascular complications (752,754).

Recent studies are helping to explain why some cancer survivors are at greater risk of cardiovascular complications after treatment. A recent study found that clonal hematopoiesis—an age-related buildup of genetic changes in blood-forming stem cells—was associated with higher risk of heart failure after cancer therapy (755). These findings suggest that testing for clonal hematopoiesis may one day help identify high-risk survivors who could benefit from closer cardiac monitoring. Researchers are also developing risk prediction models that use clinical data from electronic health records (EHRs) to identify patients at greatest risk for treatment-related cardiovascular complications and guide more targeted cardiac surveillance during and after cancer treatment (756,757).

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and often debilitating adverse effect of cancer treatment. Symptoms of CIPN include numbness, tingling, burning, painful, or electric shock–like sensations in the hands and feet that can impair daily functioning and overall quality of life (758). In severe cases, CIPN may require dose reductions or early treatment discontinuation to alleviate symptoms, potentially compromising treatment effectiveness and survival (758). While some symptoms subside over time, nearly one-third of survivors experience persistent, painful neuropathy lasting 6 months or longer after treatment completion (759).

Options for managing CIPN remain limited, as there are no medications approved by the US Food and Drug Administration (FDA) specifically for its treatment or prevention. Duloxetine, an antidepressant medication also used to treat certain types of nerve pain, is recommended by some cancer-focused organizations for treating painful CIPN, but its effects are modest (760,761). Recent studies suggest that nonpharmacologic strategies, including hand cooling with frozen gloves and compression of the hands and/or lower limbs with snug-fitting surgical gloves or compression stockings during chemotherapy, may reduce the risk of CIPN (762,763). Beyond cooling and compression, topical treatments may offer another strategy for reducing CIPN. Findings from a small randomized clinical trial suggest that a topical nociceutical cream, a medicated topical cream intended to calm or protect the skin's pain-sensing nerves, may reduce or delay CIPN among patients receiving taxane- and/or platinum-based chemotherapy (764). However, additional studies are needed to confirm the effectiveness of these approaches across broader patient populations and determine how best to implement them in routine cancer care.

Cachexia is a serious condition characterized by unintentional loss of body weight and muscle mass, weakness, and progressive functional decline in individuals with cancer or other chronic diseases. Cachexia is estimated to affect 50 percent to 80 percent of cancer patients and is associated with reduced treatment tolerance, diminished quality of life, and shorter survival. Cachexia accounts for approximately 20 percent of all cancer-related deaths and is widely recognized as an indicator of poor prognosis (765,766). Despite its severity, there are currently no FDA-approved treatments specifically for cachexia (767). However, recent research is improving understanding of the biological mechanisms underlying the condition and identifying potential therapeutic strategies.

A recent clinical trial found that ponsegromab, an investigational drug that blocks growth differentiation factor 15 (GDF-15), a protein involved in weight loss, improved body

SIDEBAR 40

Phases of Cancer Survivorship

Survivorship is a continuum that can be broken down into three phases, as shown below. The phase of survivorship depends on the type and stage of cancer, treatments received, and goals of care as determined by the patient and their care provider.

Phases	Acute Survivorship (Time of Diagnosis)	Extended Survivorship (End of Initial Treatment)	Permanent Survivorship (Long-term Surveillance)
FOCUS	Cancer treatment	Immediate effects of cancer and treatment	Long-term effects of cancer and treatment
DURATION	Weeks to months	Months to years	Several years
CHALLENGES	• Arthralgia (joint pain) • Bone density loss (osteoporosis) • Cachexia (unintentional weight loss and muscle wasting) and/or sarcopenia (loss of muscle mass and strength) • Cognitive impairment (trouble remembering, learning new things, concentrating, and/or making decisions that affect everyday life) • Development of new cancers • Distress, anxiety, and/or depression, which can interfere with a person's ability to cope effectively with cancer and its treatment • Endocrine dysfunction, referring to impairments in the hormonal system, which includes glands and organs that control vital functions such as growth, metabolism, sexual development, reproduction, sleep, and appetite • Fatigue or persistent exhaustion that is not relieved by rest • Fear of cancer recurrence • Hearing loss (ototoxicity) • Heart damage (cardiotoxicity)	• Infertility • Insomnia • Kidney dysfunction • Lung (pulmonary) damage • Lymphedema, or swelling, most often in the arms or legs, that can cause pain and interfere with daily functioning • Metabolic syndrome, defined as the presence of three or more of the following risk factors: excess abdominal fat, high blood pressure, high triglycerides, impaired fasting glucose, and low high-density lipoprotein (HDL) cholesterol • Nerve problems (including peripheral neuropathy) • Nutrition issues, such as chronic nausea, vomiting, and loss of appetite • Oral changes, including dry mouth, tooth decay, gum disease, and jaw stiffness • Pain • Premature or accelerated aging • Recurrence (return) of original cancer • Sexual dysfunction	
HOW TO COPE	• Build a strong support network • Talk with your care team about new or persistent symptoms • Adopt a healthy lifestyle • Seek psychosocial support for depression, anxiety, or other mental health needs	• Join a cancer support group • Use mindfulness to cope with long-term effects of cancer treatment • For more information, visit: www.cancer.gov/about-cancer/coping	

Although many cancer survivors face challenges, some groups are at higher risk for severe, long-term, and late effects. These groups include individuals diagnosed during childhood, adolescence or young adulthood (ages 0 to 39), as well as older adults (age 65 and older).

To address the unique needs of younger survivors, several organizations have developed survivorship guidelines for those diagnosed with cancer during childhood, adolescence, or young adulthood, including the National Comprehensive Cancer Network (NCCN) *Guidelines for Adolescent and Young Adult (AYA) Oncology* and the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*. These guidelines were developed to help standardize and improve the lifelong follow-up care of individuals diagnosed with cancer as children, adolescents, or young adults. For more information, see http://survivorshipguidelines.org/.

Older adult cancer survivors also face distinct challenges. NCCN *Guidelines for Older Adult Oncology* addresses issues specific to this population, including screening and comprehensive geriatric assessment, evaluation of treatment risks and benefits, and management of treatment-related complications.

weight, appetite, and physical activity in patients with advanced cancer (768). Ponsegromab is now being evaluated in a larger clinical trial to determine whether the drug can improve outcomes in a broader patient population (769). At the same time, emerging research is beginning to reshape how scientists understand cancer cachexia. Rather than being viewed simply as a consequence of reduced food intake, cachexia is increasingly understood as a whole-body condition in which cancer disrupts normal communication among organs and tissues (766,770,771). Early studies suggest that these disruptions may affect inflammation, metabolism, muscle, and brain function in ways that contribute to hallmark features of cachexia, including muscle loss, poor appetite, fatigue, and reduced motivation (770,772,773). These discoveries are helping researchers identify new ways to detect cachexia earlier and develop treatments that target the underlying biological drivers of the condition.

Cancer and its treatments can contribute to broader physical and functional limitations, placing survivors at increased risk for disability. Recent data show that the prevalence of disability among US cancer survivors, defined as difficulty in any of six functional activities (e.g., difficulty seeing, hearing, remembering or concentrating, walking or climbing stairs, dressing or bathing, or living independently), has increased in recent years, from 40 percent in 2016 to 46 percent in 2024 (774). This growing burden has important implications for survivors' long-term health and well-being. Studies show that functional limitations and disability among cancer survivors are associated with increased risk of mortality, greater use of emergency room services, psychological distress, and socioeconomic hardship, including employment disruption and cost-related barriers to care (775,776). These findings underscore the importance of identifying and addressing functional limitations as part of comprehensive survivorship care.

A major concern for cancer survivors is the risk of recurrence or the development of a new, biologically distinct, second primary cancer (SPC). The likelihood of developing an SPC is influenced by many factors, including the type and stage of the original cancer, treatments received, genetic predisposition, lifestyle behaviors (e.g., smoking), and socioeconomic status (777). Compared to the general population, cancer survivors face an estimated 16 percent increased risk of developing an SPC (778). This risk is particularly elevated among individuals with a history of childhood cancer, survivors of Hodgkin lymphoma, and survivors of cancers linked to obesity and tobacco use (777). Recent data also suggest that the risk of SPCs among US cancer survivors has increased substantially over the past two decades, reinforcing the importance of risk-based survivorship care and long-term surveillance (779).

Population-based data on cancer recurrence remain incomplete because recurrence information is not routinely collected by most cancer registries (780). Although the evidence is limited, available studies show that recurrence risk varies widely by cancer type, stage at diagnosis, treatments received, and age at diagnosis (781). For example, a recent study of adolescents and young adults (AYAs) with cancer found that nearly 10 percent developed metastatic recurrence, with the highest risks observed among those with sarcoma, colorectal, cervical, and breast cancers (782). As more people live longer after a cancer diagnosis, recurrence tracking has become increasingly important for understanding long-term outcomes and strengthening cancer surveillance. Researchers are developing AI-based and machine learning–based tools to identify recurrence from pathology reports, radiology reports, insurance claims, and other clinical data sources, which may help fill this gap and provide a more complete picture of outcomes after cancer diagnosis (783).

In **patients with resected nonmetastatic colorectal cancer** whose tumors carried specific *PIK3CA* gene mutations, **taking 160 mg of aspirin daily reduced the risk of cancer recurrence** by more than 50% compared to placebo.

Source: (564).

W54

As cancer treatment continues to evolve, the long-term effects of newer therapies are becoming an increasingly important focus of survivorship research. Immune checkpoint inhibitors (ICIs), a type of immunotherapy, are increasingly used to treat a wide range of cancers (see **Releasing the Brakes on the Immune System**, p. 132). While ICIs have revolutionized cancer care and improved patient survival, their use has been associated with a distinct range of side effects known as immune-related adverse events (irAEs) (784). These irAEs occur when the immune system attacks healthy tissues and can affect nearly any organ system, including the skin, endocrine organs, gastrointestinal tract, lungs, heart, kidneys, joints, and nervous system (703,785-787). Chronic irAEs, defined as those lasting more than 3 months after treatment discontinuation, may affect up to 50 percent of patients treated with ICIs, with endocrine and joint-related side effects among those most likely to become long-term (785,787).

Other novel cancer therapies are also creating new survivorship challenges. Chimeric antigen receptor (CAR) T-cell therapies can cause serious immune and neurologic side effects during treatment and may also increase the risk of infections, prolonged low blood cell counts, and SPCs (788,789). Antibody–drug conjugates and molecularly targeted therapies can also cause treatment-specific side effects, including lung inflammation, ocular toxicities, skin changes such as rash

and itching, gastrointestinal symptoms, and cardiovascular complications (790,791). As these therapies are used more widely and earlier in the course of cancer treatment, continued research is needed to better understand their long-term effects.

Advances in immune cell-based therapies are also creating new opportunities to reduce serious long-term complications of cancer treatment. In 2026, FDA approved Tregzi, a treatment made from donor immune cells that is designed to lower the risk of chronic graft-versus-host disease, a serious complication after stem cell transplant that can affect long-term health and quality of life for patients with blood cancers (792).

Psychosocial Challenges

A cancer diagnosis can pose serious challenges to an individual's mental and emotional well-being. Studies consistently show that cancer survivors experience a greater burden of mental health and psychosocial challenges than individuals without a history of cancer, including elevated risks of depression, anxiety, post-traumatic stress disorder, cognitive difficulties, and fear of cancer recurrence (793,794). These challenges may be especially pronounced in the months and early years following a cancer diagnosis, as patients navigate the psychological, physical, and practical demands of cancer care. In a large study of nearly 372,000 adults with cancer, more than 1 in 10 patients developed a new mental health disorder within the first year of diagnosis, most commonly anxiety or depressive disorders (795). These early mental health disorders were associated with a 51 percent increased risk of death in the first several years after diagnosis.

Loneliness is an increasingly common and concerning issue among cancer survivors. Recent research indicates that more than one in three survivors in the United States experience moderate to severe loneliness, particularly those with poor physical or mental health, financial hardship, or limited social support (796). These experiences can affect multiple dimensions of cancer survivorship, including health and quality of life. In a study of more than 17,000 US cancer survivors, those who reported loneliness were more likely to report poor quality of life, poor physical and mental health, severe pain, and fatigue (797). Loneliness and social isolation have also been associated with increased risk of death among patients with cancer (798).

Cancer survivors also face a higher risk of suicide than individuals without a history of cancer (799,800). Encouragingly, national data show that cancer-related suicide rates in the United States have declined over the past several decades (801,802). This decline may be attributable to advances in cancer treatment, increased availability and integration of psychosocial support and palliative care services, and more effective management of cancer-related symptoms and distress. However, these gains have not been shared equally across all survivor populations. Recent data point to concerning increases in suicide deaths among AYA cancer survivors, particularly males, highlighting the importance of age-appropriate mental health screening and suicide prevention services as part of comprehensive survivorship care (803).

Financial Challenges

Financial toxicity refers to the financial burden and distress experienced by patients and their families as a result of cancer diagnosis and treatment, as highlighted in the personal story of Shauna McLaughlin and her daughter **Madison (Maddie) Bergstrom** (see p. 150). Evidence suggests that nearly half of cancer survivors experience some degree of financial hardship, driven in part by the out-of-pocket costs associated with cancer care (804). These costs can begin immediately after diagnosis and may be especially high during the initial treatment period, even among patients with private insurance. For example, a recent study of privately insured adults (aged 18 to 64 years) found that a new diagnosis of breast, colorectal, or lung cancer was associated with nearly $4,150 in additional out-of-pocket costs during the month of diagnosis and the subsequent 6 months (805). Patients diagnosed with more advanced-stage disease experienced the highest out-of-pocket costs.

The financial burden of cancer is not experienced equally, with certain groups disproportionately affected. Cancer survivors with lower household incomes, those living in disadvantaged neighborhoods or communities, those who are uninsured or publicly insured, and individuals enrolled in high-deductible or high cost-sharing health plans are at especially high risk for financial hardship (806-808). Working-age adults may face additional challenges because cancer diagnosis and treatment can disrupt employment, leading to lost income and potential loss of employer-based health insurance (808).

Financial toxicity can have serious consequences for cancer survivors and their families. High costs of cancer care may lead patients to delay or forgo needed care because of cost, borrow

In a study of privately insured adults ages 18 to 64 with breast, colorectal, or lung cancer, **average out-of-pocket medical costs were nearly $600 higher per month** during the 6 months after diagnosis compared to adults without cancer.

Source: (805).

W55

money, accumulate debt, or file for bankruptcy to pay for care (809-812). Financial hardship is also associated with worse health outcomes, including increased depression, anxiety, pain, and higher mortality risk (813-815). These financial pressures can also affect patients' ability to meet basic needs. Evidence suggests that cancer survivors who experience medical financial hardship are more likely to report health-related social needs, including food insecurity, housing insecurity, and transportation barriers (816-818). In a recent study, adults currently undergoing cancer treatment had nearly twice the odds of housing insecurity, defined as being unable to pay rent, mortgage, or utility bills in the past year, compared to adults without a cancer history (819).

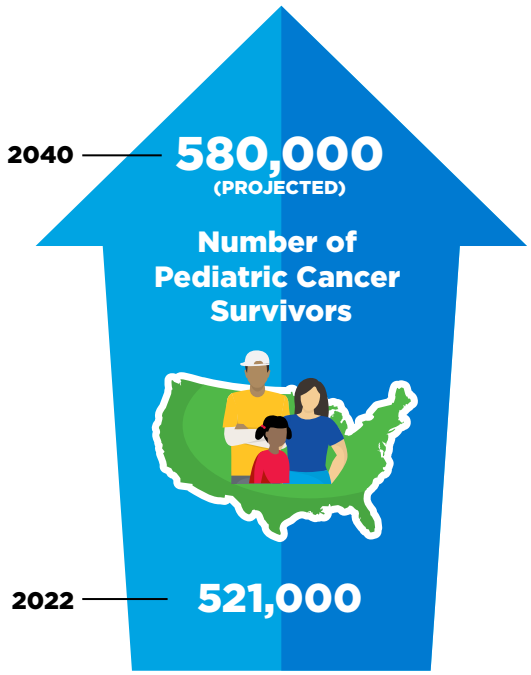
Mitigating financial toxicity will require coordinated action across health care systems, employers, policymakers, and community organizations. In oncology settings, routine screening for health-related social needs and financial hardship can help identify patients at risk and connect them with financial navigation, insurance and cost-related assistance, transportation and housing resources, and other support services (820,821). At the same time, broader policy and social support, including paid sick leave, employment protections, affordable health insurance, and housing assistance, may help patients maintain income, health insurance coverage, and financial stability during and after treatment (821-823). Together, these strategies can help reduce the financial burden of cancer and support continuity of care without compromising patients' financial security or basic needs.

Unique Challenges Faced by Vulnerable Populations

Although many cancer survivors face physical, psychosocial, and financial challenges, certain populations have unique survivorship needs that require specialized approaches to care. Factors such as age at diagnosis, developmental stage, treatment exposures, comorbid health conditions, and social determinants of health can shape survivorship outcomes and influence the type of care and support that survivors require. The following sections highlight key survivorship challenges and emerging approaches to care for childhood, adolescent and young adult, and older adult cancer survivors.

Childhood Cancer Survivors

Childhood cancer survivors include individuals of any age who were diagnosed with cancer during childhood (ages 0–14 years). In 2026, an estimated 9,680 children will be diagnosed with cancer, and over 700 will die from the disease (5). Thanks to advances in cancer treatment, the overall 5-year relative

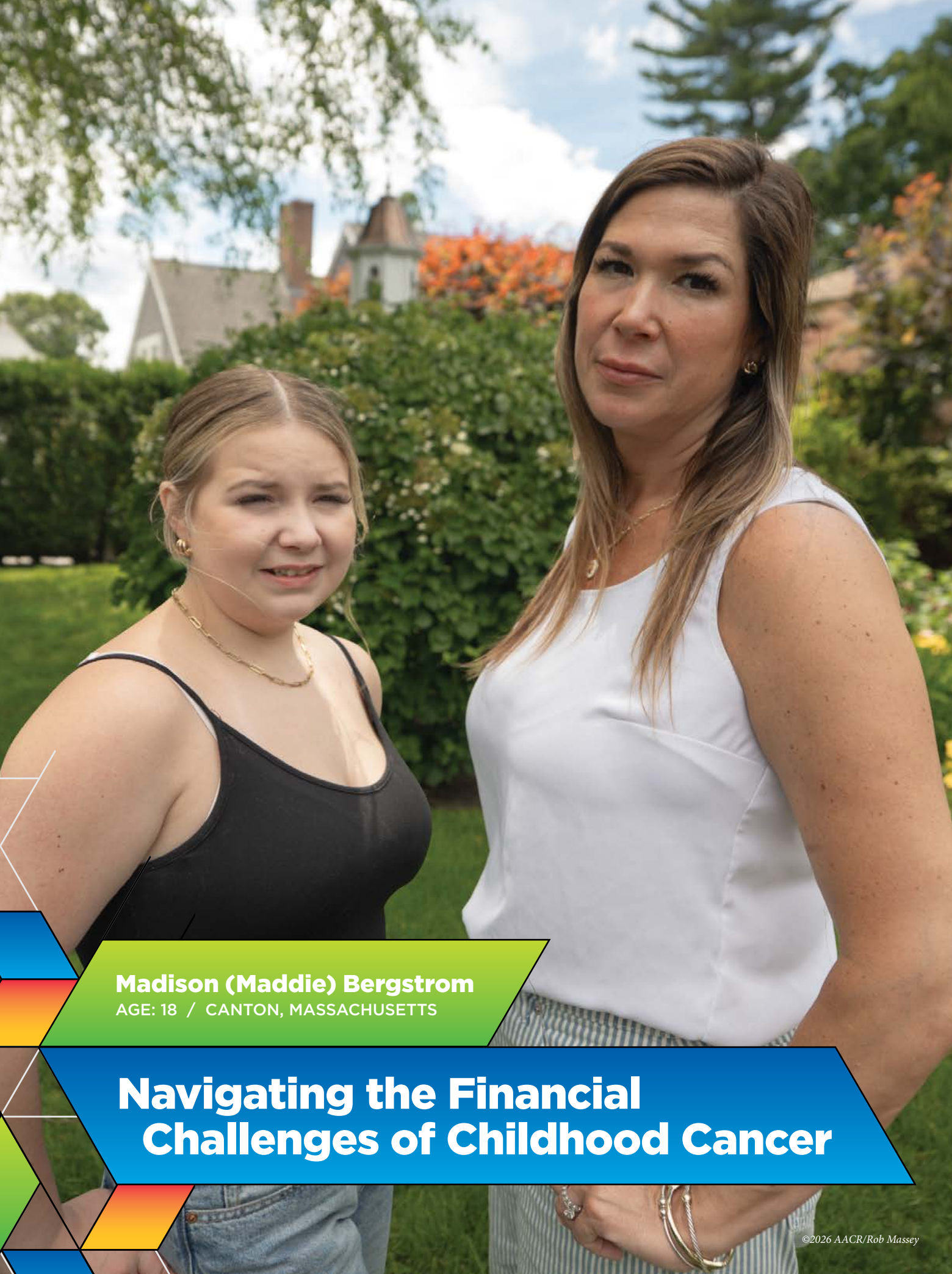


Sources: (48,825). W56

survival rate for childhood cancer has improved markedly over the past several decades, from just 58 percent in the mid-1970s to more than 85 percent today (48,824). While advances in oncology have markedly improved survival rates, childhood cancer survivors face a substantial burden of long-term and late effects because cancer and its treatment occur during critical periods of growth and development. The type and severity of these late effects depend on several factors, including the cancer type and stage at diagnosis, the specific type of treatment and doses received, as well as the survivor's age and overall health at the time of treatment.

Children treated with cisplatin chemotherapy are at increased risk of developing hearing loss, also called ototoxicity. One study found that 75 percent of children 5 years of age or younger and 48 percent of children older than 5 years experienced cisplatin-related hearing loss within 3 years of starting therapy (826). In September 2022, FDA approved sodium thiosulfate to reduce the risk of hearing loss associated with the chemotherapeutic cisplatin in pediatric patients. Sodium thiosulfate reduced the risk of cisplatin-associated hearing loss by nearly 50 percent compared to those who did not receive the drug (827). More recent analyses suggest that sodium thiosulfate may provide substantial protection among children at highest risk for hearing loss, including those younger than 5 years and those treated for hepatoblastoma, neuroblastoma, or medulloblastoma, reducing their risk by up to 80 percent to 90 percent (828).

continued on page 152



Madison (Maddie) Bergstrom
AGE: 18 / CANTON, MASSACHUSETTS

Navigating the Financial Challenges of Childhood Cancer

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A conversation with Shauna McLaughlin, Maddie's mother

In 2010, Madison (Maddie) Bergstrom was a lively toddler. When she suddenly began having belly pain, her mom, Shauna McLaughlin, noticed that Maddie's stomach looked swollen. A precautionary visit to the doctor sent them to the hospital for a stomach X-ray. Additional scans and bloodwork revealed cancer. Maddie was 19 months old.

Further testing confirmed that Maddie had B-cell acute lymphoblastic leukemia, the most common form of childhood leukemia. "I didn't expect it," Shauna recalled. "I've had gut feelings when something was wrong with my kids, but the last thing I thought I would hear was that my child had cancer."

The family spent nearly a month in the hospital before transitioning to outpatient treatment. The next 2 years were consumed by rounds of chemotherapy, frequent hospital and emergency room visits, and managing the many side effects of treatment. Shauna faced a difficult choice. "I immediately quit my job," she said. "As a parent, you have to choose between going to work or being there for your child."

The family went from two incomes to one. Gas for trips to the hospital, parking, and meals away from home all quickly added to their expenses. "When your child has cancer, your main concern is, 'Is my child going to live?'" Shauna said. "But then the afterthought is, 'Can I pay my mortgage? Do I have enough gas in my car to get to the emergency room tonight?' You make less money and incur more costs."

After 2 years of treatment, the family celebrated when Maddie was declared cancer-free. In 2013, just 6 months later, the cancer came back. By then, Shauna was raising Maddie as a single mother, and their financial situation had become even more challenging. Shauna quit her job for a second time, going from one income to no income at all.

At one point, Shauna had to borrow money from her grandmother for gas to get to the emergency room and seek charitable assistance to heat her home during a cold Massachusetts winter. Although charitable organizations helped with some expenses, most assistance was limited to one-time grants. Shauna also struggled to admit that she needed help. "As a parent, your job is to make sure you can financially support your child," she said. "When you have never been in trouble like that before, it is really hard to admit it."

After another relapse, Maddie underwent 2½ years of chemotherapy and radiation therapy. As Maddie neared the end of her treatment, Shauna had met her now-husband, Patrick. When Maddie reached remission a second time, Shauna was pregnant with their son.

Then, in 2016, just 1 week after the birth of Liam, Shauna and Patrick's son, Maddie relapsed for a third time. The family enrolled Maddie in a clinical trial at Children's Hospital of Philadelphia evaluating an experimental chimeric antigen receptor (CAR) T-cell therapy, a type of immunotherapy that reprograms a patient's own immune cells to recognize and attack cancer cells.

Maddie was one of the first 25 children in the world to receive CAR T-cell therapy. The family temporarily relocated to Philadelphia, where she received treatment and was closely monitored for potentially serious side effects. The infusion took just a single day. Maddie has been cancer-free for nearly a decade.

Today, Maddie is 18 years old and thriving. She is now a high school senior and has earned her certified nursing assistant credential. Inspired by the nurses who cared for her, Maddie plans to become a pediatric oncology nurse to help future patients. "I want to be able to say, 'I went through it. There is hope,'" Maddie said. "I just want to give back what they've given to me."

For Shauna, the years of caring for Maddie inspired advocacy. She now works with organizations focused on addressing the financial burden families face when caring for a child with cancer. Shauna serves as a parent advocate on the IGNITE Consortium, a pediatric cancer health equity research initiative co-founded by Maddie's oncologist, Dr. Kira Bona, a pediatric oncologist at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Shauna has also partnered with Family Reach, an organization dedicated to eliminating financial barriers for people with cancer, which helped her own family directly. Although her family has recovered financially, she says the recovery took years, long after Maddie's treatment ended.

Shauna has a clear message for policymakers: Funding cancer research saves lives, but families need support navigating the financial realities of treatment. "If we can lessen the toll that cancer takes on a child and their family, then we have to invest in that research," she said. "Families shouldn't have to choose between caring for their child and keeping a roof over their heads."

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

Childhood cancer survivors are also at increased risk for treatment-related cardiotoxicity, which is a major contributor to long-term morbidity and premature mortality. Anthracycline chemotherapy and radiation are well-established contributors to late cardiovascular disease, including cardiomyopathy, heart failure, coronary artery disease, valvular disease, and other cardiovascular complications (829,830). Emerging therapies, including immunotherapies and targeted agents, may introduce new cardiovascular risks that are not yet fully understood in pediatric survivor populations (831). Despite these risks, some long-term complications may be mitigated through protective strategies. For example, dexrazoxane, a cardioprotective agent given with anthracycline chemotherapy, has been associated with better heart function nearly 20 years after treatment among young adult survivors of childhood cancer (553).

SPCs are another major concern for survivors of childhood cancer and are among the most serious late effects in this population. Studies consistently show that survivors of childhood cancer have an increased risk of SPCs compared to the general population (832-835). Common SPCs among childhood cancer survivors include breast and thyroid cancers, central nervous system tumors, sarcomas, leukemia, and certain skin cancers (829,835). Prior radiation therapy is a well-established risk factor, particularly for cancers that arise in or near areas exposed to radiation, and certain chemotherapy agents have also been linked to elevated SPC risk. Emerging research also suggests that inherited genetic susceptibility and treatment-related epigenetic changes may help explain why some survivors are especially vulnerable to certain late effects, including SPCs and treatment-related cardiotoxicity (835-837).

The elevated risks of SPCs, cardiovascular disease, and other chronic conditions reflect a broader pattern of accelerated aging among survivors of childhood cancer. Accelerated aging refers to the earlier onset of chronic, age-related health conditions that typically occur later in adulthood, including cardiovascular disease, stroke, and SPCs. Among survivors of childhood cancer, accelerated aging may arise, in part, from damage caused by cancer treatments, which can damage DNA, shorten telomeres, alter epigenetic patterns, trigger chronic inflammation, and accelerate the deterioration of organs and tissues (837). Reports indicate that 60 percent to more than 90 percent of childhood survivors develop one or more chronic health conditions following their cancer diagnosis (838,839). A recent study estimated that, compared to the general population, childhood cancer survivors are nearly three times more likely to develop a serious age-related chronic health condition before age 65 (840). These risks persist into older adulthood. Among childhood cancer survivors who were alive at age 50, researchers found that the risk of SPCs, cardiovascular disease, and other severe, life-threatening, or fatal chronic health conditions remained substantially elevated as survivors aged (841).

A study of more than 1,100 young adult survivors of childhood cancer found that, compared to peers without a history of cancer, survivors were:

- **21% less likely** to have earned a college degree
- **31% less likely** to be married or partnered
- **Nearly 2 times more likely** to be unemployed
- **More than 3 times more likely** to live with a parent

Source: (842). W57

Neurocognitive late effects are also a major concern for survivors of childhood cancer. Those diagnosed or treated as young children are especially vulnerable because cancer and its treatment can coincide with periods of rapid brain development. Neurocognitive late effects may include difficulties with attention, memory, processing speed, executive function, learning, and emotional regulation (843,844). These challenges can have lasting consequences for educational attainment, employment, independent living, social integration, and financial well-being (843,845). Emerging research also suggests that some survivors may experience accelerated brain aging, which may contribute to cognitive difficulties later in life (846,847).

The challenges faced by survivors of childhood cancer also extend to psychosocial well-being, family functioning, and quality of life. Survivors of childhood cancer may experience anxiety, depression, post-traumatic stress symptoms, fear of recurrence, and concerns about late effects, infertility, or future health (848,849). These concerns can also affect parents and caregivers, who often play a central role during treatment and survivorship. In one recent study, post-traumatic stress, depression, and anxiety symptoms were reported among both childhood cancer survivors and their parents, underscoring the importance of ongoing psychosocial screening and family-centered survivorship support (848).

Adolescent and Young Adult Cancer Survivors

AYA cancer survivors are individuals who were diagnosed with cancer between the ages of 15 and 39. In 2026, an estimated 88,120 AYAs will be diagnosed with cancer in the United States, and more than 8,900 will die from the disease (850). Advances in cancer care have markedly improved outcomes for

SIDEBAR 41

Fertility and Reproductive Health After a Diagnosis of Cancer

A common adverse effect of cancer treatment is infertility, or the inability to conceive children. This may result from surgery on reproductive organs, radiation, or the effects of cancer medications on reproductive cells and can affect both male and female childhood, adolescent, and young adult (CAYA) cancer survivors. Because some fertility preservation options are most effective before cancer treatment begins, CAYA patients should discuss infertility risk and available fertility preservation options with their health care provider as early as possible after diagnosis, ideally before treatment starts.

Boys and men:

- Sperm banking
- Shielding of testes from radiation if receiving radiotherapy
- Testicular sperm extraction

Girls and women:

- Surgically moving ovaries away from areas of radiotherapy
- Removing cervix but preserving uterus
- Shielding of ovaries from radiation if receiving radiotherapy
- Banking of ovarian tissue
- Banking of eggs
- Banking of embryos

Cancer-focused organizations have established guidelines recommending that discussions of fertility preservation, as well as reproductive and sexual health, be incorporated as an essential component of cancer care, particularly for CAYA patients (857,859). However, fertility preservation rates remain lower among survivors who are Black, have lower incomes, or live in rural areas, due in part to the high costs of many fertility preservation procedures. As of June 2026, 21 states and the District of Columbia have enacted mandates requiring certain state-regulated private health plans to cover fertility preservation for individuals at risk of treatment-related infertility, including infertility resulting from anticancer therapies (861). This is an increase from July 2022, when only 12 states had such mandates.

AYAs with cancer, with 86 percent now expected to live 5 years or more after diagnosis (12).

A diagnosis of AYA cancer often occurs during a formative period when individuals are completing education, entering or advancing in the workforce, establishing financial independence, forming long-term relationships, and making decisions about fertility and family-building. Cancer and its treatment can disrupt these milestones and create lasting health, psychosocial, and financial challenges that persist into long-term survivorship (851,852).

Like survivors of childhood cancer, survivors of AYA cancer are at risk for long-term and late effects. In a recent study of long-term survivors of young adult cancer, more than 70 percent reported at least one clinically significant symptom, and nearly one-third reported four or more symptoms (853). The most commonly reported symptoms included fatigue, changes in physical appearance, cognitive problems, pain, and neuropathy. AYA survivors are also at risk for developing serious chronic health conditions earlier in life. In one analysis, nearly 40 percent of AYA survivors developed at least one chronic health condition within 10 years of diagnosis, compared to 26 percent of AYAs without cancer. Compared to those without cancer, survivors of AYA cancer also had a two- to three-fold increased risk of cardiomyopathy, stroke, chronic liver disease, and renal failure, and more than a 10-fold higher risk of hypothyroidism and avascular necrosis, a serious bone condition (854).

AYA cancer survivors also have an elevated risk of SPCs, which may be driven in part by treatment-induced accelerated aging (851,855). In one study, 5-year survivors of AYA cancer had a 25 percent higher risk of developing SPCs and a nearly two-fold higher risk of dying from SPCs compared to the general population (856).

Fertility remains a significant concern for AYA survivors, who often face lasting reproductive health challenges as a result of their treatment (see **Sidebar 41**, p. 153). Certain therapies can damage ovaries or testes, leading to early menopause, premature ovarian failure, reduced sperm production, or other changes that can affect fertility (857,858). As a result, timely counseling about fertility risks and options for fertility preservation is an important component of age-appropriate survivorship care. Current guidelines recommend that people with cancer be evaluated and counseled about reproductive risks at diagnosis and that fertility preservation options be discussed before cancer-directed therapy begins and revisited

throughout survivorship (857,859). However, access to fertility preservation for AYA patients remains suboptimal. According to a recent analysis, nearly one-third of AYA-treating community oncology practices had no male or female fertility preservation services available, and those with available services often relied on off-site referrals, potentially creating additional barriers to completing fertility preservation before treatment begins (860).

Psychosocial and mental health challenges are also common among AYA survivors. Because AYA cancer occurs during a formative period of social, emotional, and physical development, survivors may experience distress related not only to the diagnosis itself but also to disruptions in relationships, fertility, reproductive health, and future plans (851,862). Studies have found that AYA survivors are at elevated risk for emotional distress, mood and anxiety disorders, suicide, social isolation, fear of cancer recurrence, and body image concerns (851,862-864). These challenges can persist well beyond treatment. In one recent study, adult survivors of AYA cancer had the highest prevalence of lifetime psychiatric issues, use of prescription medication for anxiety or depression, and major depression, compared to adults diagnosed with cancer later in life and individuals without cancer (865). These findings underscore the importance of routine psychosocial screening and developmentally tailored mental health support throughout survivorship (851,862).

Financial hardship is also common among AYA cancer survivors, who are more likely to be uninsured or underinsured and may experience disruptions in education, employment, and early career development due to ongoing health needs or treatment-related late effects (852,867,868). These disruptions can contribute to financial strain, reduced earning potential, and long-term economic vulnerability throughout adulthood. Evidence suggests that these financial challenges can persist for years after diagnosis and affect survivors' ability to access care. In one study of long-term AYA survivors, greater financial distress was associated with higher odds of skipping or delaying survivorship care and mental health care, not filling prescriptions, and being unable to afford basic necessities (869). These findings highlight the need for routine screening for financial hardship and timely connection to financial navigation, insurance support, medication cost assistance, and other resources that can help AYA survivors maintain access to care and meet basic needs (870,871). Despite growing recognition of financial hardship among AYA survivors, access to financial navigation services remains limited. In a recent analysis of community oncology practices that treat AYA patients, most practices reported screening for financial distress, but only about half offered cancer-specific financial navigation (871).

Because of these complex and long-term health needs, survivorship care for childhood and AYA cancer survivors requires lifelong, risk-based follow-up and coordinated care to monitor late effects, support transitions from pediatric to adult health systems, and address psychosocial needs (852,872,873). In recognition of these challenges, the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* provide a standardized, evidence-based framework for survivorship care for children, adolescents, and young adults with cancer (874,875).

Although long-term follow-up guidelines exist for survivors of childhood, adolescent, and young adult cancers, many survivors do not receive recommended survivorship care because of barriers such as limited knowledge about late effects, financial and logistical challenges, fragmented transitions from pediatric to adult care, and gaps in survivorship care infrastructure (851,876,877). These challenges may be further compounded for survivors from medically underserved populations, underscoring the importance of equitable access to survivorship care and support services to optimize long-term health and well-being. Addressing these barriers is essential to improving survivorship care and improving long-term health and well-being of childhood and AYA cancer survivors.

A recent study of nearly 486,000 **adolescent and young adult cancer patients found that those living in the most economically disadvantaged neighborhoods** had an **82% higher risk of dying by suicide** than those living in the least disadvantaged neighborhoods, underscoring how **social drivers of health can shape mental health outcomes**.

Source: (866). W58

Older Adult Cancer Survivors

Older adults, defined as individuals age 65 and older, represent the fastest-growing segment of the cancer survivor population. In 2022, older adults accounted for 67 percent of all cancer survivors in the United States, and this proportion is projected to rise to 73 percent by 2040 (878,879). As the population of older cancer survivors continues to grow, so too does the need to understand and address the unique challenges they face throughout survivorship.

For older adults, cancer and its treatments occur in the context of normal aging processes and a higher burden of chronic health conditions. It is estimated that more than 90 percent of older adults with cancer have at least one chronic condition—such as cardiovascular disease, diabetes, arthritis, or obesity—and

Older adults with common metastatic cancers spent an average of 40 to 63 days receiving care outside the home during the year after diagnosis, reflecting time spent at medical appointments, getting treatment, undergoing testing, and receiving care in hospitals, emergency departments, skilled nursing facilities, or inpatient hospice settings.

Source: (887).

W59

over 30 percent live with three or more comorbidities (880). Cancer and its treatments can also increase vulnerability to geriatric conditions that may compromise independence and quality of life. Frailty—an age-related condition that can make it harder for the body to recover from illness, injury, or other health stressors—is associated with increased risk of disability, poor quality of life, and mortality among older cancer survivors (881,882). Cancer treatment can further accelerate frailty and functional decline and may contribute to the accumulation or worsening of chronic health conditions (881,883).

Polypharmacy, defined as the routine use of five or more medications, is common among older adults with cancer. Complex medication regimens used to manage both cancer-related symptoms and chronic conditions can increase the risk of adverse drug interactions, medication-related complications, and declines in physical functioning (884-886). These challenges can impair treatment management and increase the overall burden of survivorship care for older adults.

In addition to physical health challenges, older cancer survivors frequently experience psychosocial and financial burdens that can affect quality of life. Mental health conditions, such as anxiety and depression, are common among older cancer survivors and may persist or emerge years after diagnosis (888,889). Social isolation and loneliness are also prevalent among older cancer survivors and have been linked to poorer health outcomes and increased risk of death (890,891). Older cancer survivors are also vulnerable to financial toxicity despite having health insurance through Medicare (892-894). Studies show that cancer-related costs, including treatment expenses, transportation, and other out-of-pocket costs, can contribute to financial hardship, food insecurity, and difficulties meeting basic needs among older adults living with and beyond cancer (893-895).

Comprehensive geriatric assessment has emerged as a valuable tool for improving the care of older adults with cancer. Geriatric assessment provides a multidimensional evaluation of health status that can identify vulnerabilities not captured by routine oncology assessments, including functional limitations, comorbidities, cognitive impairment, medication use, and social support needs (896,897). Integrating geriatric assessment with structured evaluation of health-related social needs can help identify clinical and social risks that influence treatment tolerance and access to care, supporting a more personalized and equitable approach to survivorship care in this population.

Improving Quality of Life and Health Outcomes

Maintaining a healthy lifestyle through regular physical activity, a healthy diet, and avoiding alcohol and tobacco use is one of the most effective strategies for reducing the risk of developing cancer and other chronic diseases (see **Reducing the Risk of Cancer Development**, p. 55). Healthy lifestyle behaviors are also an important component of cancer survivorship care. A growing body of evidence shows that adopting healthy behaviors after a diagnosis of cancer can support long-term health, improve quality of life, and reduce the risk of cancer recurrence and other adverse health outcomes (898,899).

Participating in Physical Activity

Participating in physical activity is strongly associated with improved outcomes for cancer patients and survivors. According to a recent study, survivors who engaged in higher levels of leisure-time moderate to vigorous physical activity after diagnosis had a lower risk of cancer mortality across several cancer types, including bladder, endometrial, lung, and ovarian cancers (900). Notably, lung and rectal cancer survivors who did not meet physical activity guidelines (approximately 150 to 300 minutes of moderate activity per week) before diagnosis but met guidelines after diagnosis also had a lower risk of cancer mortality than those who remained inactive, suggesting that engaging in physical activity after a cancer diagnosis may still provide meaningful survival benefits. Evidence suggests that even modest levels of physical activity may be beneficial. For example, one analysis found that as little as 1 hour of aerobic exercise per week was associated with a 25 percent reduction in all-cause mortality among breast cancer survivors, while the greatest benefits were observed among those who met physical activity guidelines (901).

Structured physical activity during or after cancer treatment has been shown to improve physical function, reduce complications, shorten hospital stays, and enhance quality of life (902). In a recent clinical trial of nearly 900 colon cancer survivors who had completed adjuvant chemotherapy, those assigned to a 3-year structured exercise program that

Childhood cancer survivors who engaged in 100 to 140 minutes of vigorous physical activity per week had a **39% lower risk of developing a second primary cancer** than those who reported no vigorous physical activity.

Source: (905). W60

combined behavioral support with supervised aerobic exercise experienced a 28 percent lower risk of disease recurrence, SPC, or death, compared to survivors who received health education alone (903).

Physical activity may also improve the immune system's ability to detect and eliminate cancer cells (902). For example, a recent study of patients with esophageal cancer found that those who exercised while receiving chemotherapy had higher levels of immune cells within their tumors, consistent with a stronger antitumor immune response (904). These findings suggest that engaging in physical activity during treatment may enhance the body's ability to fight cancer, although more research is needed to determine whether these immune changes translate into improved treatment response or long-term outcomes.

Physical activity may also help reduce the burden of long-term treatment-related adverse effects. In an analysis of more than 22,000 childhood cancer survivors, lower physical activity was associated with a higher risk of SPCs, while higher physical activity was associated with reduced risk of SPCs (905). In a separate study of long-term childhood cancer survivors, nearly all participants had at least one adverse health outcome (such as osteoporosis, pain, heart problems, or depression), and higher physical fitness was associated with fewer adverse health outcomes (906).

Evidence also suggests that tailored exercise programs can support recovery and help manage treatment-related adverse effects among adult cancer survivors. In a recent study, a personalized, remotely monitored exercise intervention improved physical function and reduced fatigue among individuals undergoing surgery for lung cancer (907). Similarly, prostate cancer survivors who participated in a supervised aerobic and resistance training program experienced significant improvements in both sexual function and muscle strength (908).

Engaging in regular exercise may also support mental health and quality of life, particularly among older survivors. A recent analysis of randomized clinical trials found that exercise programs were associated with reduced symptoms of depression and anxiety and improved health-related quality of life among older adults with cancer (909). Activities that combine movement with breathing, balance, or mindfulness, such as tai chi, yoga, and qigong, appeared especially beneficial for managing depression and anxiety in this population.

Eating a Healthy Diet and Maintaining a Healthy Weight

Maintaining a healthy diet and body weight is an important component of survivorship care. Evidence suggests that survivors who more closely follow nutrition and physical activity guidelines after diagnosis have better long-term outcomes. In a recent study of survivors of obesity-related cancers, those with the highest adherence to recommended nutrition and physical activity guidelines had a 24 percent lower risk of death from any cause, a 21 percent lower risk of death from cancer, and a 33 percent lower risk of death from cardiovascular disease—a leading cause of death among cancer survivors (910,911). Survivors who improved their adherence to nutrition and physical activity guidelines after diagnosis also had a lower risk of death from any cause, suggesting that adopting healthier behaviors after cancer diagnosis may still provide meaningful survival benefits.

A healthy diet may be especially important for survivors at increased risk of long-term health problems, including those treated for cancer during childhood. Adult survivors of childhood cancer are at increased risk of premature aging and

Healthy behaviors remain a challenge for many childhood cancer survivors.

In a recent study of adult survivors of childhood cancer:

- **68%** did not meet physical activity guidelines
- **65%** had an abnormal body mass index
- **32%** reported problematic alcohol consumption
- **29%** were current or former smokers

Source: (913). W61

chronic health conditions, and recent evidence suggests that healthier dietary patterns may help reduce this risk. In a study of more than 3,300 adult survivors of childhood cancer, greater adherence to healthy dietary patterns was associated with a lower risk of premature aging (912). These findings suggest that dietary interventions may offer a modifiable strategy for promoting healthier aging among this vulnerable population.

Despite these benefits, many cancer survivors face challenges maintaining a healthy diet. A recent analysis of survivors of obesity-related cancers found that overall diet quality was suboptimal, with especially low intake of fruits, vegetables, dairy products, and protein-rich foods (914). Diet quality was lower among survivors with obesity, lower educational attainment, and those living in lower-income communities, highlighting how social and economic conditions can shape survivors' ability to maintain healthy eating patterns (see **Figure 2**, p. 22).

Food insecurity, characterized by limited or uncertain access to adequate food, is a widespread issue that affects millions of Americans, including patients with cancer. A recent study found that approximately 10 percent of cancer survivors report food insecurity (915). Moreover, survivors with food insecurity have an increased risk of death from any cause compared to their food-secure counterparts. Food and nutrition insecurity may be particularly concerning for childhood cancer survivors, who already face elevated risks of cardiovascular disease and other late effects. In one study of childhood cancer survivors, more than one in four lived in food-insecure households, and one in three experienced nutrition insecurity, defined as limited access to, availability of, or affordability of healthy foods (916). These children also had suboptimal dietary quality and high rates of cardiovascular risk factors, such as excess body weight or obesity and elevated blood pressure. These findings underscore the need to integrate screening for food and nutrition insecurity into survivorship care and connect families with resources that support healthy eating and long-term health.

Maintaining a healthy weight is another important focus of survivorship care, particularly because obesity is associated with increased risk of cancer recurrence, mortality, comorbidities, treatment-related adverse effects, and poorer quality of life among individuals with cancer. Recent evidence suggests that a remotely delivered weight management program can help survivors achieve meaningful weight loss. In a clinical trial of more than 3,100 women with breast cancer, participants were randomly assigned to receive either health education alone or health education plus a telephone-based weight loss program focused on reducing calorie intake and increasing physical activity (917). After 1 year, participants assigned to the weight loss program lost an average of nearly 5 percent of their baseline body weight, while those in the education-only control group gained an average of 1 percent of their baseline body weight. These findings highlight the potential of scalable lifestyle interventions to support healthy weight management during survivorship.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), a class of medications used to treat type 2 diabetes mellitus and obesity, are also emerging as an important area of research in cancer survivorship (see **Sidebar 15**, p. 64). Recent studies suggest that GLP-1 RAs not only are associated with clinically meaningful weight loss but may also be linked to reduced mortality in some patient populations (294,918). In a large study of women with breast cancer, GLP-1 RA use was associated with lower risk of overall mortality and reduced risk of recurrence among patients with obesity or type 2 diabetes mellitus (919). GLP-1 RAs may also have cardiovascular benefits for some cancer patients. In a recent analysis, use of GLP-1 RA medications was associated with a lower risk of cancer therapy–related cardiac dysfunction and cardiovascular events (e.g., heart failure, heart attack, and atrial fibrillation) among patients receiving cardiotoxic cancer therapies (920). However, because much of the evidence in cancer populations comes from observational studies, clinical trials are needed to determine whether GLP-1 RAs can improve long-term outcomes in cancer survivors.

Eliminating Alcohol and Tobacco Use

Cigarette smoking and other tobacco or nicotine product use remain important issues in cancer survivorship. In 2023, 15 percent of US cancer patients were current smokers at the time of diagnosis, and nearly half had a history of smoking (921). Furthermore, the use of electronic cigarettes (e-cigarettes) has increased in recent years, particularly among AYAs (see **Eliminate Tobacco Use**, p. 56). In an analysis of nearly 1,500 young adults with a history of cancer, nearly 47 percent reported ever using e-cigarettes, and among those who had ever used e-cigarettes, more than 30 percent were current users (922). Another analysis found that among cancer survivors who currently smoked traditional cigarettes, more than 60 percent also used e-cigarettes (923).

Continued smoking among cancer survivors is associated with a range of adverse health outcomes, including increased risks of recurrence and SPCs, greater treatment-related complications, reduced quality of life, and higher mortality (61,924-926). In a recent analysis, patients who smoked within 4 weeks before cancer surgery had higher odds of postoperative complications compared to those who had stopped smoking for at least 4 weeks prior to surgery (924). Among working-age cancer survivors, current smoking has also been associated with greater health-related work limitations and more missed workdays (927).

Given these risks, promoting smoking cessation is critical. For individuals with cancer, quitting smoking can have immediate

Alcohol consumption after a cancer diagnosis may increase the risk of recurrence, second primary cancers, and death. A recent study found that approximately **70% of patients continued to drink alcohol after a cancer diagnosis**, and 46% reported risky or potentially harmful alcohol use, highlighting the need to integrate routine alcohol screening and intervention into cancer care.

Sources: (932-935).

W62

and long-term benefits. In a recent analysis of 36 studies including more than 17,000 patients with cancer who smoked, quitting after diagnosis was associated with a 29 percent lower risk of death and reduced risk of recurrence (928). In another study, cancer survivors who quit smoking within 3 years of diagnosis had significantly improved survival, living a median of 4 years longer than those who continued smoking (929). Other studies have found similar survival benefits of quitting after diagnosis, including among patients with advanced-stage cancer (930). These findings suggest that smoking cessation support should be provided to all cancer survivors who smoke, regardless of cancer type or stage. Evidence also suggests that tailored cessation programs can be cost-effective, supporting broader implementation of smoking cessation interventions in oncology and survivorship care (931). Recognizing smoking cessation as an essential component of cancer care, the Commission on Cancer (CoC) recently implemented a new standard requiring accredited cancer centers to screen all patients newly diagnosed with cancer for current smoking and provide referrals for evidence-based smoking cessation treatment.

Alcohol use is an important and under-addressed issue in cancer survivorship. Alcohol is a known carcinogen (see **Figure 11**, p. 68), and excessive alcohol use among cancer survivors has been associated with depression and anxiety symptoms, poorer quality of life, higher hospital readmission rates, increased health care costs, and increased risks of cancer recurrence, SPCs, and mortality (933-935). Despite these risks, alcohol use remains common after a cancer diagnosis. According to one study, more than 70 percent of cancer survivors continued drinking alcohol after their diagnosis. Alarmingly, nearly half of survivors reported drinking at levels that exceeded recommended cancer prevention guidelines (see **Sidebar 18**, p. 69), and nearly one-third engaged in hazardous drinking (i.e., alcohol consumption that increases a person's risk of harm) (936). Recent evidence also suggests that alcohol use disorder (AUD), a condition marked by difficulty stopping or controlling alcohol use, is increasing among cancer survivors. In one study of nearly 6 million privately insured adult cancer survivors, the prevalence of AUD diagnoses increased by 83 percent between 2012 and 2021 (935).

Although few alcohol interventions have been developed specifically for cancer survivors, care providers should refer patients with AUD to evidence-based treatments, such as behavioral counseling and/or medication. Despite the availability of effective treatments, AUD treatment remains underutilized. Among cancer survivors newly diagnosed with AUD, only 14 percent initiated any form of treatment within 1 year, and fewer than 3 percent received FDA-approved AUD medications (933,935). These findings highlight the need for a more systematic approach to addressing alcohol use in survivorship care, including routine screening, risk counseling, and timely referral to treatment for survivors with excessive alcohol use or AUD.

Improving Mental Health

Given the substantial psychological burden experienced by many cancer survivors, strategies to support mental well-being are an essential component of survivorship care. Several approaches—including psychotherapy, mind–body interventions, support groups, physical activity programs, and routine screening for mental health concerns—have been shown to improve psychological outcomes and quality of life among cancer survivors (937,938).

Despite the availability of effective mental health interventions, many cancer survivors do not receive timely support because of barriers such as stigma, limited awareness of available resources, shortages of trained mental health professionals, geographic barriers, and limited integration of psychosocial services into cancer care (939). To address these challenges, researchers and clinicians are increasingly testing models that integrate psychosocial care more directly into oncology practice. One such approach is collaborative care, a team-based model that embeds mental health support within routine cancer care through coordinated collaboration among oncology teams, behavioral health specialists, social workers, and case managers (940,941). By strengthening communication across providers and linking symptom monitoring with follow-up support, collaborative care models are designed to reduce fragmentation between oncology and mental health systems.

Stepped-care models are also increasingly being used in oncology settings to deliver personalized psychosocial care that is matched to each survivor's level of need (942,943). In these models, survivors may begin with less intensive forms of support, such as education, self-management tools, or brief counseling, and receive more specialized or intensive care if

symptoms persist or worsen. Within oncology, stepped-care models have been recommended for the management of depression, anxiety, and fear of cancer recurrence in cancer patients and survivors (942). Research has also shown that stepped-care approaches can improve patient outcomes and quality of life while using health care resources more efficiently.

Recent evidence also suggests that EHR data can be used to help identify patients with mental health needs and guide follow-up care. In a recent pilot study, patients with elevated depressive symptoms were identified using EHR data and offered a flexible, self-guided digital mental health intervention; patients who received the intervention had greater improvements in depressive symptoms and quality of life than those who received usual care (944). In another study, EHRs were used to collect patient-reported symptoms and guide follow-up care through symptom surveillance and collaborative care (940). Compared to symptom surveillance alone, the combined model reduced overall symptom burden among oncology patients, with the most consistent benefits observed for anxiety and depression, and was associated with fewer hospital stays, emergency department visits, and intensive care unit admissions.

Despite the substantial emotional distress associated with cancer diagnosis and treatment, many survivors also report personal growth, a greater sense of meaning, or positive psychological change after diagnosis. Resilience, defined as the capacity to adapt and recover in the face of adversity, has emerged as a key protective factor for individuals facing cancer (see **Sidebar 42**, p. 160) (945). Research suggests that resilience can help buffer the effects of depression and other psychological challenges and may play an important role in supporting quality of life among people with cancer (946).

Psychosocial interventions that focus on enhancing resilience by teaching certain skills, such as mindfulness, gratitude, goal-setting, and cognitive reframing, have shown promise in reducing distress and promoting long-term psychological well-being among individuals with cancer. In a recent clinical trial, a structured problem-solving skills intervention for young adults newly diagnosed with cancer reduced depression and anxiety and improved health-related quality of life (949). Other resilience-focused interventions have been associated with increased hope and greater engagement in goals-of-care discussions among AYAs with advanced cancer (948).

Together, these advances highlight the importance of moving beyond simply identifying mental health concerns toward ensuring that survivors are connected to the right level of support at the right time. Improving mental health among cancer survivors will require routine and proactive identification of symptoms, evidence-based psychosocial interventions, stepped and collaborative care models that match support to survivor needs, and scalable approaches that can be integrated into routine oncology care.

Integrating Supportive Care

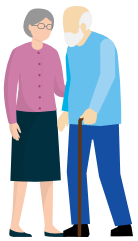
Supportive care aims to prevent and manage the adverse effects of cancer and its treatment across the entire cancer care continuum, from diagnosis through survivorship and end-of-life care (950). Palliative care is a component of supportive care that focuses on improving quality of life for individuals with cancer and their families (see **Sidebar 43**, p. 161). The goal of palliative care is to prevent or treat symptoms of disease and side effects of treatment as early as possible, while also addressing related psychological, social, and spiritual challenges. Importantly, palliative care is appropriate at any stage of disease and can be provided alongside curative treatment. Supportive care also includes hospice services. In contrast to palliative care, hospice refers to care provided near the end of life, when treatment is no longer aimed at cure and the focus shifts to comfort, symptom management, caregiver support, and alignment of care with patients' end-of-life priorities (951,952). Research suggests that supportive care is most effective when delivered by multidisciplinary teams comprising physicians, nurses, psychologists, nutritionists, pharmacists, social workers, chaplains, and other health care professionals.

A growing body of evidence supports the early integration of palliative care into oncology care. Recent analyses have found that early palliative care is associated with improved quality of life, reduced symptom burden, and improved psychological well-being among patients with cancer (953,954). Early palliative care can also help patients and caregivers navigate the uncertainty of modern cancer treatment, improve understanding of prognosis, and support care planning that aligns with patients' goals, values, and preferences (955).

The early integration of palliative care is particularly relevant for individuals living with advanced or metastatic cancer, who may experience prolonged treatment, persistent symptoms, prognostic uncertainty, and complex care decisions. As therapeutic advances

Quality of life is a leading priority for older adults with advanced cancer.

A recent study found that **more than 70% of older adults with advanced cancer prioritized maintaining quality of life over living longer**, underscoring the importance of aligning treatment decisions with patient goals.



Source: (960).

W63

SIDEBAR 42

Cancer Survivorship Experience and Resilience

Resilience refers to the process of harnessing internal and external resources to sustain well-being in the face of stress or adversity, such as a cancer diagnosis and its aftermath (945). Resilience is not a fixed trait but a dynamic process that can be fostered and strengthened over time. In survivorship, resilience plays a vital role in helping individuals cope with change, derive meaning from their experiences, and foster psychological healing.

Core Components of Resilience

Resilience is supported by a dynamic set of resources that can be cultivated and strengthened through targeted interventions. These resources fall into three broad categories:

INDIVIDUAL RESOURCES

Individual resilience resources include personal characteristics and learned skills that support emotional stability and coping. These include traits such as grit and self-efficacy, as well as skills such as stress management and goal-setting.

SOCIAL OR COMMUNITY-BASED RESOURCES

Social resilience resources involve the presence and quality of supportive relationships and social networks. Examples include access to and involvement in community-based organizations, social networks, and close relationships with family and/or peers.

EXISTENTIAL RESOURCES

Existential resilience resources represent the tools individuals use to find meaning and purpose in the face of adversity. Existential resources include faith, spirituality, positive reframing, and the ability to find gratitude.

These components are not mutually exclusive. Survivors often use a combination of resources that evolve over time and can be enhanced through supportive interventions.

Key Outcomes of Resilience-based Interventions

Evidence from clinical trials and psychosocial research suggests that resilience can be taught and enhanced through structured interventions (945,947,948).

RESILIENCE-BASED INTERVENTIONS HAVE BEEN SHOWN TO:

- Decrease anxiety and depression
- Increase positive affect, hope, meaning, and purpose
- Improve quality of life and psychosocial functioning
- Enhance engagement in care and decision-making

Importantly, resilience is a skill that can be taught, practiced, and strengthened across the cancer continuum. These interventions offer survivors an empowering path to regain control and thrive in the face of adversity.

extend survival for some patients with advanced and metastatic cancers, there is an increasing need for integrated care models that reflect the reality of living longer with an incurable disease and address quality of life throughout the illness trajectory (956-958). Early referral to specialized palliative care is recommended for patients with advanced cancer and has been shown to enhance quality of life, improve symptom management, and increase communication about goals of care and end-of-life preferences (959).

Recent studies also underscore the importance of aligning care with patients' goals and preferences. In one recent study of older adults with advanced cancer, most participants prioritized maintaining quality of life over extending survival, yet treatment patterns and outcomes did not appear to differ by patient preference, suggesting that oncology care may not always be fully responsive to what matters most to patients (960). Another study found that among patients with advanced cancer who said they preferred care focused on comfort and symptom relief rather

SIDEBAR 43

Palliative Care

Palliative care is specialized care that provides an extra layer of support to patients with serious illnesses such as cancer, as well as 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 provided near the end of life, when the focus of care shifts to comfort and quality of life, is often referred to as hospice care.

Palliative care can be given alongside curative treatment or when curative treatment is no longer an option. 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.

than extending life, more than one-third reported receiving treatment that did not align with their stated goals (961).

This disconnect can be especially consequential near the end of life, when care that does not reflect patient preferences can compromise quality of life and increase distress for patients and families. In a recent study of Medicare beneficiaries with advanced cancer, nearly 50 percent experienced at least one indicator of potentially aggressive care in the last 30 days of life, while uptake of supportive care services, including palliative care, hospice, and advance care planning, remained low (962). These findings underscore the importance of ongoing communication, advance care planning, and care models that help ensure treatment decisions reflect patients' values.

Stepped-care models are increasingly being used in oncology settings to deliver scalable, personalized care tailored to each survivor's level of need. Research has shown that a stepped-care model for delivering palliative care to patients with advanced lung cancer can effectively improve patient outcomes and quality of life, while using fewer health care resources (963). Telehealth-based palliative care has also shown promise as an effective strategy for expanding access among patients who face geographic, transportation, or other barriers to in-person specialty care (964).

Integrating supportive care into standard oncology care represents a meaningful step toward more patient-centered, responsive, and effective cancer care. As the population of people living with and beyond advanced cancer continues to grow, supportive and palliative care models must be introduced earlier, delivered equitably, and designed to align care with patients' symptoms, goals, values, and quality-of-life priorities.

Delivering Care to Cancer Survivors

As the number of cancer survivors continues to grow, ensuring access to high-quality survivorship care has become an increasingly important priority. Effective survivorship care extends beyond monitoring for recurrence and late effects and requires coordinated, patient-centered approaches that address survivors' physical, psychosocial, and practical care needs throughout the cancer continuum. The following sections describe strategies to improve care delivery, enhance continuity of care, and incorporate patient perspectives into survivorship research and clinical practice.

Coordinating Care

The multifaceted 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 and psychosocial challenges, and gaining access to other survivorship resources. While many of these services exist, survivors often face difficulties navigating the health care system to find and utilize them. Effective coordination of care is essential to help survivors identify and access the resources they need to maintain their health and well-being.

Patient navigators and clinical care coordinators are individuals who help cancer patients and survivors access resources more effectively (see **Sidebar 44**, p. 162). Evidence from a recent study found that community-focused patient navigation programs helped increase trust in health care providers, reduced system-level barriers, and improved continuity of care, particularly among medically underserved populations (965). One such program, the Integrated Cancer Care Access

SIDEBAR 44

Patient Navigation for Cancer Survivors

The first patient navigation program in the United States was developed to address racial disparities in breast cancer screening and follow-up among Black women. Implementation of this program was associated with a 70 percent increase in 5-year survival in this population (967). Although patient navigation is increasingly recognized as an effective strategy to support cancer survivors, challenges in implementation and access remain.

Benefits

Patient navigation plays a critical role in addressing gaps in care and supporting diverse patient needs across the cancer care continuum. Evidence shows that patient navigation:

- Improves access to screening, patient care coordination, symptom management, and follow-up care (965,968,969).
- Lowers the cost of health care by reducing emergency room visits and missed appointments (970,971).
- Decreases financial toxicity for patients with cancer (971,972).

What Has Been Done?

In recognition of the benefits of patient navigators, legislative efforts have been made to increase access to patient navigation, including:

- **The American College of Surgeons Commission on Cancer requires all accredited organizations to have a patient navigation program.** The Community Preventive Services Task Force also recommends the use of patient navigation services to increase cancer screenings among historically disadvantaged racial and ethnic populations and people with lower incomes.
- **In 2024, the Centers for Medicare and Medicaid Services (CMS) introduced new Medicare billing codes** that support reimbursement for patient navigation services for individuals with serious illnesses, including cancer. These changes recognize the important role of nonclinical personnel, including patient navigators and community health workers, in supporting patients (973).
- **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 expand access to patient navigation programs for cancer patients and survivors.

Challenges

Despite the benefits of patient navigators, several barriers limit the reach and effectiveness of patient navigation:

- The organization and training of patient navigators in the United States is highly variable. Lack of standardization can lead to different experiences for survivors.
- Despite recent policy changes, there remains substantial confusion regarding eligibility, coverage, and reimbursement of patient navigation services across Medicare, Medicaid, and private insurers.
- Patient navigation services are typically not well integrated into electronic health information systems, which are designed to support care coordination by improving access to patient history and clinical information. This results in poor coordination and delayed information sharing among patient navigators.

Addressing gaps in standardization, reimbursement, and system integration is essential to realizing the full potential of patient navigation to improve survivorship outcomes and reduce disparities.

Network (ICCAN), is a multidisciplinary initiative that provides one-on-one, culturally and linguistically tailored navigation and assistance with essential needs, such as food, housing, and financial support, for underserved cancer patients (966). Research on ICCAN demonstrated that patients who received these services experienced significantly higher treatment completion rates and greater improvements in quality of life compared to those receiving standard care.

Survivorship care plans (SCPs) are another important tool for improving care coordination. These plans typically include a summary of the patient's diagnosis and treatment, along with guidance for follow-up care, including recommended health screenings, surveillance for recurrence and second cancers, and management of long-term and late effects. By facilitating communication among patients, primary care providers (PCPs), and oncologists, SCPs help ensure coordinated, continuous care as patients transition from active treatment to long-term survivorship.

SCPs have been shown to improve several aspects of survivorship care delivery and patient outcomes. Survivors who receive SCPs are more likely to adhere to recommended surveillance and screening for second primary cancers and other late effects (974-976). SCPs have also been shown to improve survivors' knowledge of their cancer history and follow-up care needs and enhance self-efficacy and confidence in managing survivorship care (977). These improvements in care delivery and patient engagement are increasingly recognized as important mechanisms through which SCPs may influence longer-term outcomes. A recent study found that SCP receipt was associated with a 38 percent lower risk of death among childhood cancer survivors (978).

Incorporating SCPs into EHRs can further improve care continuity by making survivorship information accessible across clinical teams. Several studies recommend integrating SCP templates into EHR systems to foster care coordination among oncologists, PCPs, and patients (979,980). Recent work highlights the need for dynamic, EHR-enabled care plans that can be updated over time, shared across oncology and primary care teams, and used to track key aspects of survivorship care, including follow-up, prevention, chronic disease management, and patient reported outcomes (980).

PCPs are increasingly recognized as essential partners in cancer survivorship because they are well positioned to manage comorbidities, deliver preventive care, and support survivors' long-term health and well-being. However, a recent study found that only 43 percent of cancer survivors maintained regular PCP visits 5 to 7 years after diagnosis (981). Younger survivors and those diagnosed with advanced-stage cancers were less likely to maintain PCP engagement compared to older survivors and those diagnosed at earlier stages, suggesting that these groups may be especially vulnerable to gaps in survivorship care and unmet health needs. Notably, survivors who remained engaged with an oncologist during this period were more than twice as likely to maintain regular PCP visits as those without ongoing oncology care, suggesting that stronger integration between oncology and primary care may help close critical gaps in long-term survivorship care (981).

Recent studies have identified several promising strategies for strengthening coordination between oncology and primary care. In one safety-net health system, EHR data helped identify cancer survivors with chronic conditions who could benefit from primary care follow-up, and an oncology nurse coordinator helped connect these patients to primary care during active treatment, improving patient-reported care coordination (982). Another emerging approach is to integrate primary care into oncology settings. For example, one tertiary cancer center established an oncology primary care clinic that provided ongoing, survivorship-informed primary care for patients with active cancer or a history of cancer, helping to improve continuity of care and strengthen coordination between oncology and primary care teams (983).

Despite growing recognition of survivorship as a distinct phase of cancer care, survivorship care delivery remains fragmented and variable across health systems. To address these gaps, NCI, in collaboration with the US Department of Veterans Affairs and other stakeholders, recently established national standards for cancer survivorship care (984). These standards provide a framework for developing comprehensive survivorship programs, organizing services, evaluating their impact, and ensuring that survivors have access to high-quality, coordinated care across diverse settings.

However, meeting these standards will require addressing key workforce challenges. In addition to persistent shortages of oncologists and PCPs, there are currently no accredited training programs in cancer survivorship, limiting efforts to standardize care and train the next generation of providers (985). Expanding access to survivorship services will require greater investment in training and supporting multidisciplinary care teams, including clinicians, patient navigators, primary care clinicians, social workers, behavioral health providers, and other professionals who are essential to delivering high-quality survivorship care.

Leveraging Patient Reported Outcomes

Patient reported outcomes (PROs), which are reports provided directly by patients about their health, symptoms, and daily functioning, are increasingly recognized as essential tools in clinical trials as well as routine practice (see **Sidebar 45**, p. 164). PROs provide critical insights into patient symptoms, functional status, and quality of life, enabling a more comprehensive understanding of treatment tolerability and overall well-being (986).

SIDEBAR 45

Patient Reported Outcomes

Patient reported outcomes (PROs) are reports given by patients on changes in quality of life or functional status associated with health care or treatment. PROs are captured using patient-reported measures, such as self-reported surveys and questionnaires, that collect information on symptoms, daily functioning, and overall well-being. PROs aim to make cancer research and clinical care more patient-centric.

- PROs are **not interpreted by a physician** or anyone else and are a direct reflection of a patient's experience.
- PROs **capture information on health-related quality of life, functional status, symptom severity, emotional health** (such as anxiety or depression), and **experiences with care**.
- In clinical trials, PROs are **essential for understanding how treatments impact patients** beyond clinical measures, including how well or poorly treatments are being tolerated.
- Pharmaceutical companies increasingly use PROs in **drug development** to prioritize patient experiences and ensure treatments are safe, tolerable, and aligned with patients' needs.

PROs are collected through questionnaires, which alert clinicians to the status of the patient regarding quality of life, symptoms, and health-related behaviors (e.g., smoking, diet, and physical activity). When paired with automated alerts in clinical care, these systems can prompt timely interventions by health care providers. Evidence from large-scale trials shows that patients who participate in regular symptom monitoring experience better clinical outcomes, including improved symptom control, better quality of life, and fewer emergency department visits and hospitalizations (987-990). In a recent study of children with advanced cancer, integrating weekly electronic PRO reports into pediatric palliative care helped clinicians identify and respond to symptoms, leading to improvements in overall and physical quality of life (991).

Emerging evidence also suggests that PROs can provide important insights into a patient's overall prognosis. A recent systematic review and meta-analysis found that patients' self-reported quality of life, physical functioning, and symptom burden were associated with overall survival, even after accounting for clinical factors (992). These findings suggest that PROs may help clinicians better understand a patient's overall health and identify those who may need additional support.

The integration of PROs with EHRs and real-time alert systems has proven both feasible and effective across diverse clinical settings. In a recent clinical trial, EHR-integrated PRO systems not only supported more responsive care but also improved communication between patients and providers (990).

Despite the clear benefits, barriers to widespread adoption of PROs remain, including clinician skepticism, technological limitations, workflow integration challenges, and disparities in digital access and literacy (993). Overcoming these barriers will require coordinated efforts to invest in user-friendly technology, provide training for clinicians and patients, streamline integration into clinical workflows, and ensure equitable access to digital tools across diverse patient populations.

Incorporating PROs into standard cancer care represents a meaningful step toward more patient-centered, responsive, and effective cancer care. By systematically capturing patients' experiences and symptoms, PROs can inform clinical decision-making, facilitate timely interventions, and help ensure that care remains aligned with patients' needs, priorities, and goals.

Supporting Caregivers

Caregivers comprise family members and/or friends who help patients with long-term chronic illness and manage any and all aspects of their care. In 2025, an estimated 63 million US adults provided care for another person, representing nearly one-quarter of all adults in the United States (994). It is further estimated that more than four million of these caregivers were supporting an adult with cancer.

Cancer caregivers play a critical role across the cancer care continuum, helping patients manage medications, coordinate appointments, monitor symptoms, communicate with health care teams, and advocate for additional care when needed (994,995). Although these responsibilities are essential to patient care, they can place considerable strain on caregivers, resulting in emotional, physical, and financial burdens that negatively affect their quality of life.

The demands of caregiving may also contribute to adverse health outcomes among caregivers. One study found that first-degree relatives and spouses of patients with genitourinary cancers had a 10 percent increased risk of developing a psychological illness and a 28 percent increased risk of cardiovascular disease

(996). Other studies indicate that up to 40 percent of cancer caregivers meet criteria for clinically significant traumatic stress or depression (997). Recent evidence also suggests that family caregivers of patients with cancer have an elevated risk of suicidality, particularly when caring for patients with aggressive cancers and during the years following a cancer diagnosis (998). These findings highlight the need to integrate caregiver distress screening, psychosocial support, and referral pathways into routine oncology care.

Emerging research highlights the interdependence of patient and caregiver experiences. In a study of cancer survivors and their caregivers, caregiver anxiety and depressive symptoms predicted subsequent psychological distress among survivors, underscoring the extent to which caregiver well-being may shape patients' emotional health during treatment (999). The relationship between patient and caregiver distress was especially pronounced when survivors had high symptom burden or limited social support and when caregivers experienced social isolation or limited social support, highlighting the importance of addressing psychosocial needs among both patients and caregivers rather than focusing on either group in isolation.

Moreover, caregivers often face substantial social and financial challenges. These include transportation barriers, job and/or academic disruptions, and unmet psychosocial needs. For example, employment disruptions, such as unpaid leave, job loss, or reduced hours, are common among caregivers, often resulting in loss of income and health insurance (1000). Recognizing the reciprocal nature of the patient–caregiver relationship is essential for delivering equitable, comprehensive, and person-centered oncology services. Addressing caregiver needs through proactive screening for unmet needs, tailored psychosocial interventions, and financial support is critical to improving outcomes for both caregivers and the patients they support.

Cancer survivors who provide care to others represent a particularly vulnerable population, with substantial health and psychosocial support needs. A national analysis found that nearly one in five cancer survivors reported caregiving responsibilities and that these survivors were more than twice as likely to experience moderate to severe psychological distress as survivors without caregiving responsibilities (1001,1002). These individuals are also more likely to report unmet social needs, including food, housing, or transportation insecurity, compared to survivors who were not caregivers, suggesting that caregiving responsibilities may compound the social and economic burdens already faced by cancer survivors (1003). Despite reporting higher levels of unmet social needs, many survivors with caregiving responsibilities report that they do not feel comfortable discussing these challenges with health care providers, highlighting the need for more proactive screening for unmet social needs and targeted support for this vulnerable population (1003).

Enacted in more than 40 states, the Caregiver Advise, Record, and Enable (CARE) Act of 2016 requires hospitals to identify a caregiver for every patient and provide them with resources and training prior to releasing the loved one from the hospital. In 2022, the US Department of Health and Human Services released the National Strategy to Support Family Caregivers. Developed through a multi-agency collaboration with private-sector partners, the strategy outlines more than 500 actions to strengthen caregiver support across five key areas: recognition and inclusion, access to services, financial and workplace protections, caregiver engagement, and data-driven policy development (1004). Despite growing recognition of caregiver needs, nearly a quarter of CoC-accredited US cancer centers do not have a family caregiver program, underscoring the need to strengthen caregiver support in oncology settings (1005).

Envisioning the Future of Cancer Research

IN THIS SECTION, YOU WILL LEARN:

- Artificial intelligence approaches are accelerating scientific discovery, streamlining drug development, improving clinical decision-making, and enabling more personalized cancer care.
- Liquid biopsies are transforming cancer detection and treatment by providing minimally invasive, real-time insights that enable early detection, treatment selection, and continuous monitoring of disease.
- Cancer vaccines are expanding precision immunotherapy by preventing cancer in high-risk individuals and training the immune system to recognize and eliminate existing tumors.
- RNA medicines are emerging as a powerful new class of programmable therapeutics that can precisely regulate gene expression and deliver highly targeted cancer treatments.

The pace of progress against cancer has accelerated tremendously in recent years. Breakthrough discoveries and technological advances across the fields of medicine have substantially increased our understanding of cancer initiation and progression. This foundational knowledge is driving better strategies to reduce the risk of developing cancer, detect cancer at the earliest possible stage, and treat cancer effectively and more precisely—with fewer long-term side effects. As a result, cancer deaths are declining, and cancer survivors are living longer and fuller lives.

The extraordinary opportunities to translate our growing understanding of cancer biology into more precise and effective therapies are a source of great optimism for cancer researchers, including **AACR President 2026–2027, Keith T. Flaherty, MD, FAACR** (see p. 168).

Below, we highlight some of the most exciting areas in cancer science and medicine that are poised to transform the future of cancer research and patient care.

A New Wave of Technologies

Emerging technologies are driving progress in cancer research by enabling scientists to investigate tumors with greater precision (see **Sidebar 8**, p. 41). For example, single-cell multi-omics and computational approaches are allowing researchers to simultaneously map the genetic and functional states of individual cells, offering new insights into tumor evolution, the tumor microenvironment, and the mechanisms that influence cancer development and treatment resistance (1006). Technologies such as organoid systems, miniature organ-like structures grown from a patient's own tumor cells, and three-dimensional (3D) bioprinted models (see **Sidebar 4**, p. 33) are advancing our understanding of the disease by more closely mimicking cancer biology and accelerating the development of more effective, personalized therapies (1007-1009). The sections below highlight some of the most promising emerging technologies in cancer research.

Artificial Intelligence

Artificial intelligence (AI) has the potential to transform cancer research and patient care by enabling faster, more accurate, and personalized approaches across the cancer continuum. AI technologies, including machine learning, deep learning, generative AI, large language models, and agentic AI, are now being applied to tasks such as analyzing histopathology images, identifying genomic alterations, and discovering new drug candidates (see **Sidebar 46**, p. 167).

continued on page 170

SIDEBAR 46

Understanding Artificial Intelligence and Its Impact on Cancer Research and Care

Artificial intelligence (AI)

AI is the ability of a computer to perform tasks commonly associated with human intelligence, such as learning, reasoning, and problem solving.

MACHINE LEARNING (ML)

A type of AI that allows systems to learn and perform tasks without being explicitly programmed. The more comprehensive and representative the data provided to an ML model, the better its performance is likely to be.

DEEP LEARNING (DL)

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.

GENERATIVE AI (GenAI)

An ML method, often powered by DL, that uses learned data patterns to generate new content, such as text and images.

LARGE LANGUAGE MODEL (LLM)

A type of GenAI trained on massive text datasets to understand and generate human-like language. A well-known application of an LLM is ChatGPT, which uses this technology to answer questions, hold conversations, and produce text on a wide range of topics.

AGENTIC AI

A type of AI capable of autonomously setting goals, planning multistep actions, interacting with tools or environments, and adapting to feedback.

AI technologies are advancing all aspects of cancer research and patient care.

Improving Detection and Diagnosis

SCREENING AND EARLY DETECTION: Analyzing scans, pathology slides, and blood samples to rapidly detect cancer earlier and more accurately.

CANCER PROFILING: Classifying cancer subtypes and predicting outcomes using multi-omic and image data, potentially reducing expensive molecular testing.

Advancing New Treatments

UNCOVERING CANCER VULNERABILITIES: Detecting molecular drivers and structural features in tumor biology that can be therapeutically targeted.

DRUG DISCOVERY: Analyzing molecular interactions to design novel compounds and repurpose existing drugs.

DESIGNING TREATMENT COMBINATIONS: Integrating analyses of drug response data and clinical outcomes to suggest therapy combinations predicted to be more effective or less toxic.

Accelerating Basic Research Discoveries

GENOMIC PATTERN RECOGNITION: Analyzing large-scale genomic datasets to uncover fundamental mechanisms of cancer initiation and progression.

POPULATION-LEVEL INSIGHTS: Identifying patterns in epidemiologic, environmental, and clinical data to inform cancer risk, disparities, and prevention strategies.

Enhancing Clinical Decision-making

CLINICAL TRIALS: Matching patients to trials based on clinical criteria and generating virtual control arms using real-world data to improve trial efficiency and inclusivity.

VIRTUAL PATIENT MODELING: Creating digital twins, virtual representations of patients, to simulate disease progression and guide personalized treatment planning.

EVALUATING PATIENT OUTCOMES: Predicting survival, relapse, or therapy response.

PRESIDENT'S VISION

Envisioning the Next Era of Cancer Medicine Through Biological Discoveries

Keith T. Flaherty, MD, FAACR
AACR PRESIDENT 2026–2027
Director of Clinical Research, Richard Saltonstall Endowed Chair in Oncology, Mass General Brigham Cancer Institute; Professor of Medicine, Harvard Medical School, Boston, Massachusetts

Over the course of my 25-year career as a physician-scientist, I have witnessed a remarkable transformation in our understanding of cancer and how we diagnose and treat patients, as reflected in the *AACR Cancer Progress Report 2026* and the 15 previous editions. One of the biggest advances has been our ability to decode the cancer genome. Around the turn of the millennium, we began sequencing entire cancer genomes, and at nearly the same time, the approval of imatinib (Gleevec) demonstrated that identifying a specific molecular alteration could create a "lock-and-key" for targeted therapy, paving the way for more precise treatments matched to each patient's cancer. That breakthrough unleashed a new generation of discoveries that continue to transform cancer medicine today.

Cancer remains one of the most complex human diseases. A single cell contains roughly 20,000 protein-encoding genes, and only a subset of those genes and pathways are co-opted by cancer to drive disease. Our challenge is not simply to catalog what is altered, but to determine which alterations truly matter, which requires years of investigation by a broad community of researchers working across disciplines. The future of cancer research will depend on our ability to reduce that complexity into actionable knowledge to create new therapeutic opportunities.

Beyond our growing genetic understanding of cancer, one of the most important advances over the past two decades has been uncovering how cancers evade the immune system. Foundational discoveries revealing the immune checkpoints—molecular "gas pedals" and "brakes" that regulate immune cells—led to therapies targeting the PD-1/PD-L1 pathway. These treatments have transformed outcomes for many patients with advanced solid tumors, allowing a subset of individuals who once faced fatal diseases to achieve long-term survival. Similarly, engineered cellular therapies have produced extraordinary results for many patients with hematologic malignancies. Together, these advances demonstrate how deep biological understanding can fundamentally reshape cancer treatment.

Our growing understanding of cancer biology is also revealing new opportunities for therapeutic innovation in areas such as epigenetic regulation, metabolic reprogramming, and the tumor microenvironment. Cancer cells interact with immune cells, fibroblasts, blood vessels, and many other cell types within the tumor microenvironment that contribute to cancer development. Understanding these interactions will create new opportunities for therapeutic intervention and more rational combination therapies. The growing understanding of cancer–immune interactions is also fueling renewed optimism for cancer vaccines, where early clinical results suggest exciting possibilities for the future.

The technologies available to cancer researchers have also advanced at an unprecedented pace. We can now characterize DNA, RNA, proteins, and even individual cells within a patient's tumor in extraordinary detail. These advances have generated an enormous volume of information—far more than any individual investigator can fully interpret. Artificial intelligence (AI) offers an opportunity to overcome this challenge by integrating these complex datasets and uncovering biological and clinical patterns that would otherwise remain hidden. I believe AI will become an indispensable partner in translating increasingly sophisticated molecular data to improve diagnoses and identify new therapeutic strategies.

Scientific progress must also extend beyond biology to ensure that every patient benefits from these discoveries. As outlined in the *AACR Cancer Disparities Progress Report 2026*, disparities in cancer outcomes are driven, in large

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"We stand at a point where we have the greatest ever insight into the complexities of cancer, and we're on the verge of translating that understanding into entirely new therapeutic approaches."

part, by unequal access to screening, diagnosis, molecular testing, and cutting-edge therapies. As new technologies—including blood-based cancer detection and AI-assisted diagnostics—enable earlier detection and increasingly personalized treatments, addressing these disparities becomes even more urgent. Solving these challenges will require collaboration among basic scientists, translational investigators, clinicians, population scientists, and implementation researchers to identify practical solutions that improve access and outcomes for all patients.

One of AACR's greatest strengths is its ability to convene the broad cancer research community around shared scientific goals. AACR Project GENIE®, for example, has demonstrated the power of that approach by pooling clinical and molecular data across institutions, creating a resource that enables discoveries no single center could achieve alone. More recently, AACR established the Center for Cancer Clinical Trials to leverage the diversity and expertise of its members in designing and executing multicenter investigator-initiated clinical trials. Together, these efforts illustrate how AACR's unique role as a convener can accelerate discoveries and help translate them into better outcomes for patients.

We stand at a defining moment in cancer research. Decades of sustained investment have produced an unprecedented understanding of cancer biology, powerful new technologies, and a growing ability to translate discovery into improved patient care. Now is not the time to slow that momentum. Continued public investment in medical research, combined with support for the next generation of cancer scientists, will allow us to capitalize on the extraordinary foundation that has already been built. If we sustain that commitment, I believe we will usher in an era in which increasingly precise, biology-driven approaches will continue to transform the lives of patients with cancer.

Scan the QR code
to watch Dr. Flaherty's video interview.

Researchers are also using AI to analyze complex biological data and amplify the capabilities of other emerging research technologies to accelerate basic research discoveries (see **Technological Innovations and Collaborative Science**, p. 50). For example, researchers recently combined AI with advanced spatial imaging technologies to generate high-resolution maps of tumors, revealing the spatial organization and interactions of cancer and immune cells within the tumor microenvironment (1010).

Advances in AI approaches have already begun to demonstrate benefit in cancer screening and early detection (see **Advances in AI-assisted Screening Approaches**, p. 91). AI is improving the interpretation of routine medical images, including computed tomography (CT) and magnetic resonance imaging (MRI) scans, allowing earlier detection and characterization of cancers that are hard to diagnose and treat, such as pancreatic cancer and glioma (1011,1012). Additionally, AI methods allow more accurate analysis of complex digital images of tissue samples without requiring extensive manual annotation, increasing the efficiency and interpretability of digital pathology workflows (1013).

AI is reshaping cancer drug development by streamlining aspects of cancer science and medicine that have traditionally been time-consuming, expensive, and high-risk. By analyzing vast datasets, modeling complex biological systems, and uncovering meaningful insights, AI is helping researchers identify key drivers of disease and design new therapies more efficiently. These innovations have the potential to accelerate drug discovery while delivering safer, more targeted treatments to patients.

Early drug development involves identifying molecules that can interact with proteins that drive cancer and other diseases (see **Sidebar 25**, p. 99). Despite decades of advances in drug discovery, approximately 90 percent of druggable disease targets remain without small-molecule therapies. One recently developed AI model enabled genome-wide virtual drug screening by rapidly screening hundreds of millions of small molecules against protein binding sites. Using this approach, researchers screened approximately 10,000 human proteins against more than 500 million compounds, identifying more than two million candidate molecules (1015).

After 30 days of **using an ambient AI scribe**, a tool that generates clinical notes from patient visits, **burnout among clinicians fell from 52% to 39%**.

Source: (1014).

W64

Another recent advance is a generative AI model that designs novel small-molecule drug candidates tailored to the characteristics of individual cancers. This model creates novel compounds predicted to be effective against specific genetic alterations while also identifying the genes and biological pathways they are likely to target. This approach demonstrates the potential for AI to accelerate precision drug discovery by rapidly generating personalized drug candidates for cancers that currently lack effective treatments (1016).

AI models can also predict the mechanisms of action of anticancer drugs by integrating functional genomic data with drug response profiles. In one study, researchers developed a model that identified primary and secondary drug targets, predicted context-specific drug responses across different genetic backgrounds and tissue types, and generated target profiles for 1,500 cancer-related drugs (1017).

Moreover, AI approaches can accelerate the identification of effective drug combinations. An open-source platform that combines automated high-throughput screening with machine learning was recently developed to evaluate drug combinations. The study presented one of the largest drug combination screens in a single model system to date, screening more than 9,000 drug combinations in a neuroblastoma cell line, substantially reducing the experimental time and resources needed to identify promising therapeutic combinations (1018).

AI can also expand treatment options for cancer through drug repurposing—the use of existing or previously developed drugs for new therapeutic purposes. Researchers recently developed an AI system that uses large language models to support drug repurposing for non–small cell lung cancer. By analyzing more than 10,000 published clinical case reports across multiple candidate drugs, the system accurately identified clinically relevant evidence for repurposed therapies while extracting information on patient demographics, treatment responses, and outcomes. This approach demonstrates how AI can overcome time- and labor-intensive manual review and curation of real-world data to identify drug repurposing candidates supported by clinical evidence (1019).

These findings highlight how AI models can help overcome long-standing barriers in drug discovery by narrowing down large experimental workflows, uncovering clinically relevant therapeutic opportunities, and guiding the development of more personalized cancer treatments.

AI-driven technologies are also improving clinicians' ability to predict patient outcomes, personalize treatment plans, and enhance clinical trial design (see **Innovations in Cancer Clinical Trials**, p. 100). Digital twins—virtual, continuously updated models of individual patients—are one such technology. Digital twins integrate real-world data from electronic health records and clinical evaluations,

alongside multi-omic and lifestyle information, to simulate disease progression, predict treatment responses, and guide personalized treatment based on a patient's own unique biology. They also show promise in clinical trial settings, particularly for pediatric and other rare cancers, where they can function as synthetic control arms to augment or replace conventional controls when patient enrollment is limited.

Another emerging application for AI is assisting clinicians in complex surgical planning and decision-making. In a recent study, an AI model improved preoperative planning for glioblastoma surgery by predicting how much of a patient's tumor could be safely removed (1020). Further, AI has shown potential in supporting decision-making during surgery. By combining molecular imaging with machine learning–based imaging analysis, researchers were able to rapidly distinguish between malignant and benign lung nodules in real time (1021).

AI is also streamlining radiation treatment planning. In a recent study, an AI-based radiotherapy planning system generated high-quality treatment plans across multiple cancer types, typically within 5 minutes. More than 80 percent of the AI-generated treatment plans were deemed clinically acceptable by physicians, and 60 percent were preferred over manual plans (1022).

Muscle-invasive bladder cancer is an aggressive form of bladder cancer in which the tumor grows into the muscle layer of the bladder wall. Because of its higher risk of spreading beyond the bladder, patients are often given chemotherapy before surgery to shrink the tumor and eliminate cancer cells that may have spread. However, not all patients respond to this treatment, which can cause serious side effects. Researchers have recently developed a machine learning model that integrates gene expression data with digital pathology images to predict how patients will respond to chemotherapy. The model identified biomarkers that accurately predicted treatment response across multiple patient cohorts and showed that these predictions were associated with improved patient survival (1023). This approach is much less expensive than molecular assessment of gene expression and may help tailor treatment plans for patients and reduce unnecessary exposure to toxic therapies.

As AI begins to reshape cancer research and patient care, it introduces new layers of complexity that can both help and hinder clinical decision-making, raising serious concerns about fairness, transparency, and accountability. AI systems require rigorous validation, continuous performance monitoring, and standardized governance before they can be safely integrated into routine clinical practice. Without consistent evaluation across diverse patient populations and clinical settings, AI tools may perform well in one institution but fail to generalize to broader use. However, efforts to ensure broad inclusion and oversight extend beyond technical validation. There is a need for shared responsibility between AI developers, regulators, and health care institutions to address bias and avoid discriminatory outcomes from AI-powered decision tools while ensuring that clinicians remain actively involved in evaluating and overseeing AI-generated recommendations (1024).

Liquid Biopsy

A biopsy involves the removal of cells or tissues from a patient to help physicians diagnose a condition, such as cancer, or assess how it is responding to treatment. Traditionally, biopsies are invasive and limited to a single timepoint. In contrast, a liquid biopsy—the analysis of blood or other body fluids—offers a less invasive alternative by capturing tumor-derived material that is routinely shed into the bloodstream during cancer development and treatment. This material includes circulating tumor cells and cell-free DNA (cfDNA), such as circulating tumor DNA (ctDNA).

Although they are currently used primarily alongside traditional tissue biopsies, liquid biopsies may also be useful for detecting tumors located in areas that are difficult to biopsy. Unlike traditional biopsies, liquid biopsies can be easily repeated during the course of clinical care, which may enable dynamic, real-time insights into tumor evolution and therapeutic responses.

Researchers are increasingly extracting biological information from the fragmentation patterns of cfDNA, an emerging field known as fragmentomics (1025). Recent advances are further expanding the information obtainable from cfDNA through fragmentomic analyses to infer tissue of origin, gene expression patterns, epigenetic features, and cancer-associated genomic alterations (1026). These approaches have improved the performance of liquid biopsies for applications such as multi-cancer early detection (see **Advances in Minimally Invasive Screening Approaches**, p. 92) and disease characterization (1027).

Additionally, liquid biopsy approaches can enhance diagnosis, treatment selection, and monitoring of disease progression and recurrence (see **Sidebar 47**, p. 172). Liquid biopsy can be used to guide treatment selection by identifying genomic alterations that can inform precision medicine approaches. In a recent study of patients with advanced solid tumors enrolled in the NCI-MATCH (Molecular Analysis for Therapy Choice) trial, ctDNA testing showed high concordance with tissue sequencing for detecting actionable genomic alterations, supporting its use to identify patients eligible for molecularly matched therapies (1028). Further, research shows that integrating tissue and liquid biopsy together provides even more comprehensive genomic profiling and that patients with concordant findings across both experience improved clinical outcomes with molecularly matched therapies (1029).

SIDEBAR 47

Liquid Biopsy

Liquid biopsy is a minimally invasive technique that analyzes cancer-derived material, such as circulating tumor DNA (ctDNA), in blood or other body fluids. It offers real-time insight into a patient's tumor, enabling early detection, treatment monitoring, and prediction of disease progression.

These methods can be either tumor-informed, requiring sequencing of a patient's tumor to identify and track personalized mutations, or tumor-agnostic, using standardized panels to detect common cancer-related mutations found across different tumor types.

How Liquid Biopsies Are Used in Cancer Care

MULTI-CANCER EARLY DETECTION (MCED)

Liquid biopsy platforms can screen for multiple cancers simultaneously by analyzing ctDNA patterns and methylation signatures.

PREDICTING METASTASES

Early identification of ctDNA can signal future spread of cancer before imaging detects it.

PREDICTING PRIMARY OR ACQUIRED RESISTANCE

Detection of mutations or copy number changes in ctDNA can predict primary or acquired resistance to therapy.

TREATMENT RESPONSE MONITORING

Measuring changes in ctDNA levels over time can assess if a treatment is working.

MINIMAL RESIDUAL DISEASE (MRD)

Detection of ctDNA after treatment can reveal small amounts of cancer that remain.

RECURRENCE DETECTION

Rising ctDNA levels can signal recurrence earlier than imaging.

Liquid Biopsy Tests Can Help...

- **Overcome certain structural barriers**, such as geographic accessibility, because they do not require large-scale infrastructure and can be performed at a local clinic.
- **Detect multiple cancers** early and simultaneously.
- **Monitor if cancer has returned** in patients who have already received cancer treatment.
- **Reduce potential physical harms associated with a medical procedure**, because these tests are minimally invasive.
- **Inform treatment decisions**, because they can be used to quickly determine a patient's response to treatment and to detect the emergence of drug resistance.

However, Liquid Biopsy Tests May...

- **Lead to higher rates of false-positive findings and unnecessary follow-up procedures** when used to detect multiple cancers. Follow-up procedures can be costly and invasive with their own side effects and may increase anxiety for patients and strain for health care systems.
- **Be out of reach for medically underserved populations** because of costs and access.
- **Produce false-negative results** in early-stage cancers or when tumors shed little DNA into the bloodstream, potentially delaying diagnosis or misinforming treatment decisions.
- **Not yield the same benefit for all populations** if all populations are not well represented in the research leading to the development of such tests.

Beyond selecting therapies, liquid biopsy is also emerging as a tool for predicting which patients are most likely to benefit from immunotherapy and other treatments (see **Advances in Treatment With Immunotherapeutics**, p. 131). In a recent study of patients with breast cancer, researchers identified a blood-based immune biomarker using liquid biopsy and

LIQUID BIOPSY CAN DETECT IMMUNE-RELATED ORGAN DAMAGE
IN PATIENTS RECEIVING
IMMUNE CHECKPOINT INHIBITOR THERAPY
DAYS TO MONTHS BEFORE SYMPTOMS APPEAR

Source: (707). W65

transcriptomic profiling that accurately predicted response to the addition of immunotherapy to neoadjuvant chemotherapy (1030). These findings demonstrate the potential for minimally invasive blood-based monitoring to identify patients most likely to benefit from immunotherapy while sparing others from unnecessary treatment and toxicity.

Monitoring dynamic ctDNA changes during treatment can provide early signals of treatment response or emerging resistance. In locally advanced rectal cancer, early clearance of ctDNA following chemotherapy was linked to better outcomes, while persistent ctDNA predicted poor response (1031). In another study of patients with prostate cancer, increasing ctDNA levels early during chemotherapy treatment was indicative of shorter survival and linked to treatment resistance (1032).

An emerging application of liquid biopsy that holds significant promise for improving cancer care is its ability to detect minimal residual disease (MRD) and recurrence after treatment. Recent research has demonstrated that the presence or absence of ctDNA following treatment can serve as a powerful indicator of recurrence risk and help guide posttreatment decisions.

Recent clinical trials have now shown that ctDNA can be used to guide adjuvant therapy by identifying patients most likely to benefit from additional treatment. In a recent trial of patients with muscle-invasive bladder cancer, ctDNA testing after surgery identified patients who benefited from adjuvant immunotherapy, while those who remained ctDNA-negative had high disease-free survival and favorable outcomes without additional treatment (1033). In another trial of patients with colon cancer, patients without detectable ctDNA after surgery safely received less intensive chemotherapy with fewer treatment-related hospitalizations, while those with detectable ctDNA had a higher risk of recurrence (1034).

Liquid biopsy can also be a valuable tool for long-term surveillance after curative treatment. In patients with melanoma, postoperative ctDNA detection during serial follow-up was the strongest predictor of recurrence, outperforming conventional clinicopathologic factors. Patients with detectable ctDNA at any point after surgery were significantly more likely to experience recurrence, highlighting the potential of continuous ctDNA monitoring to detect relapse early and support more personalized posttreatment surveillance (1035).

Although liquid biopsy has shown promise in enhancing current methods of cancer detection and monitoring, challenges remain that limit its routine clinical use (see **Sidebar 47**, p. 172). Researchers have highlighted key barriers to ctDNA adoption, some of which include a variable amount of detectable material and lack of standardized protocols (1036). Overcoming these hurdles through continued research will be essential to fully unlock the potential of liquid biopsies to personalize cancer care and guided treatment.

New Frontiers in Cancer Treatment

In recent years, researchers have made remarkable progress in transforming how cancer is treated. Advances in drug delivery technologies, such as engineered nanoparticles, have demonstrated their ability to improve drug stability and reduce toxicity while delivering therapeutic molecules to specific tissues and cells (1037,1038). Ongoing efforts in nanoparticle engineering will further improve the delivery of new therapies that can overcome biological barriers, accumulate within tumors, and reach their intended targets.

Another area of rapid gains has been in KRAS-targeted therapies, whereby decades of basic research have paved the way for the next generation of treatment advances (see **Basic Research Decoding Cancer's Complexities**, p. 34). Building on the success of FDA-approved inhibitors of KRAS protein with the G12C mutation, researchers are now developing molecules that target other *KRAS* mutations and degrade KRAS proteins entirely, as well as immune-based strategies—such as vaccines, engineered T cells, and combination treatments—to help the immune system better recognize and attack *KRAS*-driven cancers (see **Sidebar 48**, p. 174). The sections below highlight some of the most exciting emerging areas in cancer treatment.

Cancer Vaccines

Researchers are developing new types of cancer vaccines that prevent cancer in high-risk individuals and treat existing disease by training the immune system to recognize and attack tumor-specific targets.

Vaccines play a critical role in disease prevention, with vaccines against the hepatitis B virus (HBV) and human papillomavirus (HPV) already reducing the global burden of liver and cervical cancers by targeting oncogenic viruses before cancer develops (see **Prevent and Eliminate Infection From Cancer-causing Pathogens**, p. 71). Building on these successes, researchers are now exploring the development

SIDEBAR 48

Next-generation KRAS Therapies

KRAS (Kirsten rat sarcoma viral oncogene homolog) is one of the most frequently mutated genes in cancer. It provides instructions for making a protein that acts like an "on/off switch" to control how cells grow and divide. In healthy cells, KRAS turns on when bound to a molecule called GTP and turns off when bound to GDP. Special helper proteins (called GAPs) assist with turning KRAS off when it is no longer needed. However, when *KRAS* is mutated, as in many lung, colorectal, and pancreatic cancers, it can get stuck in the "on" position, driving uncontrolled cell growth and cancer progression. Common mutations include G12C, G12D, and G12V.

So far, only two KRAS-targeted therapeutics, sotorasib and adagrasib, have been FDA-approved, and both specifically target the G12C mutation. Now, researchers are developing a new generation of KRAS-targeted therapies that aim to block additional mutations, destroy the KRAS protein, engage the immune system, and improve outcomes through combination approaches.

KRAS-targeted Small Molecules

IMPROVED G12C INHIBITORS: These G12C-targeted inhibitors aim to work more effectively, last longer in the body, and reduce the risk of cancer becoming resistant.

BEYOND G12C: These inhibitors are being developed to target cancers driven by other common *KRAS* mutations, such as G12D, G12V, and G13D.

SYNTHETIC GAP ACTIVATORS: These drugs aim to reactivate the normal "off switch" in mutant KRAS proteins, helping to shut down their cancer-promoting activity.

RAS(ON) TRI-COMPLEX INHIBITORS: These inhibitors block RAS proteins when they are in their active, GTP-bound "on" state by forming a three-part complex that stops it from signaling.

PAN-RAS "BREAKERS": These drugs disrupt cancer-driving signals by blocking key steps that all RAS proteins (KRAS, NRAS, and HRAS) need to function, rather than targeting a specific mutation.

Targeted KRAS Degradation

PROTEOLYSIS-TARGETING CHIMERAS (PROTACS) AND MOLECULAR GLUES: These drugs tag mutant KRAS proteins for destruction by the cell's own protein-cleanup machinery.

PAN-RAS DEGRADERS: These drugs aim to eliminate multiple types of RAS proteins at once, preventing *KRAS*-driven cancers from finding a way to resist treatment by switching to another RAS family member.

KRAS-targeted Immunotherapies

KRAS INHIBITORS AS IMMUNE MODULATORS: KRAS inhibitors can also make tumors more visible to the immune system by reducing immune-suppressing signals.

T-CELL RECEPTOR (TCR) AND CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPIES: These therapies engineer a patient's own T cells to find and destroy cancer cells with specific *KRAS* mutations.

MULTI-EPITOPE PEPTIDE VACCINES: These vaccines target several *KRAS* mutations at once to create a broader and more powerful immune response.

DENDRITIC CELL (DC) VACCINES: These vaccines can teach immune cells to recognize and attack cancer cells carrying *KRAS* mutations.

Combination and Synergistic Therapies

WITH CHEMOTHERAPY OR HORMONE THERAPY: Combining KRAS-targeted therapies with standard treatments can help kill more cancer cells and prevent resistance.

WITH IMMUNE CHECKPOINT BLOCKADE: Combining KRAS-targeted therapies with immunotherapies can boost immune activity and help the effects last longer.

MICROENVIRONMENT MODULATION: Targeting the tumor microenvironment can help KRAS-targeted therapies reach cancer cells more easily and support immune cell entry.

of vaccines that target genetic mutations or molecular characteristics associated with cancer in high-risk individuals as part of broader cancer interception strategies aimed at preventing cancer before it develops (see **Advances in Genomics-based and Risk-stratified Precision Approaches**, p. 93, and **Table 4**, p. 96).

Therapeutic cancer vaccines activate a patient's immune system to recognize and destroy cancer after it has developed, often by targeting unique markers found on cancer cells. These vaccines can complement existing therapies and may be especially effective when used in combination with immune checkpoint inhibitors, chemotherapy, or molecularly targeted therapies (1039). The only FDA-approved therapeutic cancer vaccine currently is sipuleucel-T (Provenge), which was approved in 2010 for treating advanced prostate cancer.

One therapeutic cancer vaccine strategy being evaluated in clinical trials uses an RNA-based approach that can be tailored to encode multiple tumor-specific neoantigens, mutated proteins unique to cancer cells, such as the individualized pancreatic cancer vaccine trial in which **Donna Gustafson** (see p. 176) participated.

In a 5-year follow-up study, patients with high-risk melanoma who had their cancer surgically removed, and who received an individualized mRNA neoantigen vaccine alongside immunotherapy, experienced sustained improvements in recurrence-free and distant metastasis–free survival compared to immunotherapy alone (1040).

Personalized neoantigen vaccines are also being evaluated following surgery to reduce the risk of recurrence. In patients with early-stage triple-negative breast cancer, an individualized mRNA vaccine generated durable neoantigen-specific T-cell responses, with most patients remaining relapse-free for up to 6 years after vaccination (1041). Personalized vaccines are also being explored for difficult-to-treat cancers with few effective immunotherapy options. In a phase I trial of patients with glioblastoma, a personalized DNA vaccine, using up to 40 neoantigens per patient, given after surgery and radiation, induced vaccine-specific T-cell responses in nearly all patients and showed encouraging preliminary clinical outcomes (1042).

Shared-antigen vaccines, which target mutations or proteins commonly found across many patients' tumors, are also showing promising results. In patients with pancreatic and colorectal cancers who have MRD after standard treatment, a lymph node–targeted vaccine against mutant KRAS generated durable and sustained immune responses, with stronger vaccine-induced immune responses correlating with better clinical outcomes (101).

As researchers continue to improve vaccine design, identify new tumor-specific targets, and optimize combinations with other therapies, cancer vaccines have the potential to become an important component of precision cancer prevention and treatment.

Key Milestones in the Development of Therapeutic Cancer Vaccines

1990s Identification of tumor-specific antigens lays the foundation for the development of therapeutic cancer vaccines

2010 FDA approves sipuleucel-T (Provenge), the first therapeutic cancer vaccine, for the treatment of advanced prostate cancer

2017 Personalized neoantigen vaccines induce promising immune responses in first-in-human phase I clinical trials in patients with melanoma

2024 Personalized neoantigen vaccines combined with immunotherapy improve clinical outcomes in patients with melanoma

2025 Early-phase clinical trials demonstrate encouraging results for personalized and shared-antigen vaccines in patients with breast, kidney, pancreatic, and colorectal cancers

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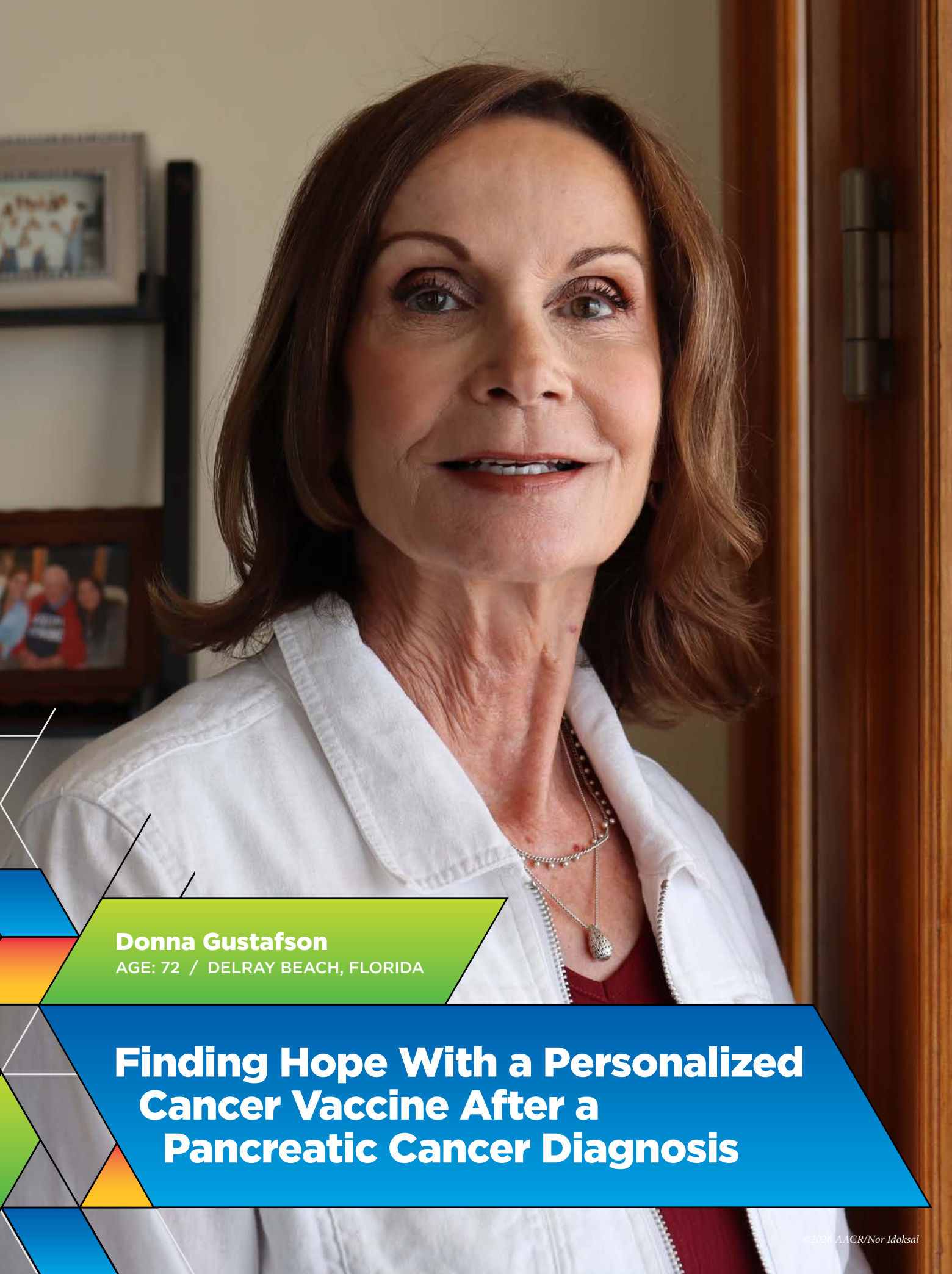
RNA Medicines

RNA molecules play essential roles in regulating gene expression, protein production, and many of the cellular processes that become dysregulated during cancer development (see **RNA Variations**, p. 43). Researchers are now harnessing these functions to develop programmable RNA molecules to treat cancer by directing cells to produce therapeutic proteins, silencing cancer-promoting genes, and stimulating immune responses. The recent success of mRNA vaccines has accelerated broader interest in RNA as a therapeutic platform (see **Cancer Vaccines**, p. 173), but RNA medicines extend far beyond vaccines.

continued on page 178



Donna Gustafson
AGE: 72 / DELRAY BEACH, FLORIDA

Finding Hope With a Personalized Cancer Vaccine After a Pancreatic Cancer Diagnosis

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At 65, Donna Gustafson was enjoying the life she and her husband, Ed, had built together over more than five decades of marriage. Surrounded by their three daughters and growing family of grandchildren, Donna split her time between Lavallette, New Jersey, and Delray Beach, Florida.

In December 2019, Donna and Ed traveled to Sydney, Australia, to spend time with their daughter and her family. After a grueling 22-hour flight, Donna felt unusually fatigued but assumed it was simply jet lag. A day or two after arriving, she developed jaundice. Believing she was dehydrated, she went to a local emergency room where she received devastating news.

"They told me that I had pancreatic cancer," Donna recalled. "I was shocked. Prior to this, I was completely healthy." When she asked about her odds, the physician told her the survival rate for people with pancreatic cancer was in the single digits. She would later learn that her pancreatic cancer was stage IIB.

Donna and Ed immediately returned to the United States. Donna was still en route home when her daughters sprang into action. "I have three amazing daughters. They are true warriors and they went into battle mode," Donna said. They researched specialists, explored available treatment options, and secured an appointment with pancreatic cancer expert Dr. Eileen O'Reilly at Memorial Sloan Kettering Cancer Center (MSK) in New York City.

During her consultation, Donna learned that she was eligible for a phase I clinical trial led by MSK evaluating a personalized cancer vaccine called autogene cevumeran. Unlike vaccines designed to prevent disease, this therapeutic vaccine would be created using information from Donna's tumor to train her immune system to find and kill cancer cells. The decision was easy. "Pancreatic cancer is often a death sentence. I knew that statistically, the odds were against me," Donna said. "The choice was a no-brainer. They were handing us hope."

Ten days later, Donna underwent a Whipple procedure, a major surgery commonly used to remove pancreatic tumors. In February 2020, as she began the clinical trial, the COVID-19 pandemic swept through New York City. Donna and her family, who had temporarily relocated to be near MSK, eventually had to continue part of her treatment closer to home at an MSK satellite location in Monmouth County, New Jersey.

Donna was the first patients to receive this vaccine for pancreatic cancer. She received vaccine treatments weekly for 8 weeks before starting 11 rounds of chemotherapy given every other week. She received a final vaccine dose after completing chemotherapy. The vaccine caused very few side effects. "I felt absolutely nothing the first couple of treatments. I was concerned, 'Is this working?'" she recalled. "But they reassured me that it was." Chemotherapy proved more difficult, but Donna leaned on support from her husband, daughters, extended family, and care team. "It was difficult," she said, "But it was doable. We just kept putting one foot in front of the other."

Donna's response to the vaccine was extraordinary. It has now been more than 6 years since her treatment. Donna has no evidence of disease, and her body continues to show a strong immune response.

Donna's life today looks remarkably similar to the one she enjoyed before cancer. She still undergoes follow-up imaging once a year but has no dietary restrictions or physical limitations. Since her treatment, Donna has celebrated her 50th wedding anniversary and welcomed two more grandchildren. She has also traveled to Sicily, hiked Mount Etna, and fulfilled a longtime dream of skydiving. "Once you're given time, you realize how precious it is," she said. "For me and my family, this has been nothing short of a miracle."

Donna hopes her experience will help others appreciate the lifesaving potential of therapeutic cancer vaccines. "I don't believe I'd be here today if it wasn't for this vaccine," she said. She also encourages eligible patients to consider participating in clinical trials. "If anyone is lucky enough to qualify for one of these trials, I would strongly encourage them to," she said. "You have nothing to lose and hope to gain."

Donna's experience shows the transformative potential of cancer research. It also underscores the need for sustained investment to accelerate progress against pancreatic cancer, a disease that has historically had very few effective treatment options. "When I looked at the statistics 7 years ago, there really wasn't a good story out there," she said. "Now, there is such hope. We need the funding. We need the research to bring this to the public and make it available to everyone."

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

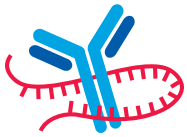
Different RNA-based approaches—including mRNA, small interfering RNA (siRNA), microRNA (miRNA), RNA aptamers (short RNA molecules that bind specific molecular targets), and circular RNA (circRNA)—can act through complementary mechanisms to alter cancer biology (1043,1044).

A major advantage of RNA medicines is that they can be rapidly designed once a molecular target is identified. For example, mRNA can instruct cells to make therapeutic proteins, siRNA can reduce production of cancer-promoting proteins, and RNA aptamers can bind specific molecular targets or deliver therapeutic cargo. Advances in RNA chemistry, chemical modification, and delivery technologies have improved RNA stability, reduced unwanted immune activation, and increased the ability of RNA molecules to reach target cells (1043).

Several classes of RNA medicines are already advancing through preclinical and clinical development. For example, miRNA-based therapeutics are being developed to restore the activity of tumor suppressor miRNAs or inhibit oncogenic miRNAs (1045). At the same time, researchers are exploring other RNA platforms that can temporarily program cells to produce therapeutic proteins directly within tumors.

An emerging approach uses circRNA, a circular form of RNA that is more resistant to degradation and can support prolonged protein production. In a recent study, researchers engineered circRNA to encode an enzyme that converts an inactive drug into toxic metabolites within tumors. Intratumoral delivery of this circRNA produced prolonged protein expression and slowed tumor growth with minimal systemic toxicity. The researchers also engineered a second circRNA encoding interleukin-15 (IL-15), an immune-stimulating molecule that can activate cancer-fighting immune cells. Combining both circRNAs enhanced immune activation and suppressed progression of advanced melanoma in preclinical models (1046).

Therapeutic RNA delivered by a tumor-targeting antibody accumulated 1,500-fold more in tumor cells than normal cells and **tripled survival in preclinical models of pancreatic cancer**.



Source: (1047).

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Despite advances, one challenge for RNA medicines is that RNA molecules are unstable and easily degraded, limiting how long they remain active in the body. Another major challenge is delivering RNA safely and selectively into tumors after systemic administration. Lipid nanoparticles and other delivery systems have helped move the field forward, but tumor-specific delivery remains a major barrier, particularly for cancers located in difficult-to-reach tissues (1043,1044).

RNA-based medicine is rapidly emerging as a new class of cancer therapeutics. However, important challenges remain, including improving targeted delivery, ensuring durable and controllable therapeutic activity, and minimizing off-target effects. Continued innovation in RNA chemistry and delivery will be essential to realize the full potential of RNA medicines and translate them into effective cancer treatments.

Advancing Cancer Science and Medical Research Through Evidence-based Policies

IN THIS SECTION, YOU WILL LEARN:

- Sustained federal investment in cancer research and its workforce drives scientific discovery and medical innovation that improve outcomes for patients.
- Evidence-based regulatory science helps bring safe and effective cancer therapies to patients as quickly as possible.
- Cancer prevention, screening, and tobacco control policies can reduce cancer risk, detect cancer earlier, and save lives.
- Science-driven policies can expand access to care, strengthen public health programs, reduce cancer disparities, and help ensure that progress against cancer reaches every patient.
- Advances in digital health, data sharing, and artificial intelligence are reshaping cancer research, treatment, and survivorship.

Investing in Research to Achieve a Healthier Future

The progress described throughout this report was not inevitable. It was built over decades through sustained federal investment, bipartisan commitment, and a research system capable of turning scientific discoveries into better prevention and earlier detection, more effective treatments, and longer survival. Through the National Institutes of Health (NIH), the National Cancer Institute (NCI), and other federal science and public health agencies, the United States (US) has helped make extraordinary advances possible for patients with cancer and their families. Sustaining that progress will require continued investment, the timely and predictable award and administration of appropriated funds as Congress intended, and a federal grantmaking process that remains grounded in scientific merit.

The results of this national commitment are clear. Since 1991, the overall cancer death rate in the United States has fallen by 35 percent, translating to more than 4.8 million fewer cancer deaths. Today, more than 18.6 million Americans are living with a history of cancer, and patients diagnosed with many types of cancer are living longer, healthier lives than was possible a generation ago. These gains reflect decades of scientific discovery, the dedication of generations of researchers, and bipartisan leadership that has sustained cancer research as a national priority.

At the center of this progress are NIH and NCI. NIH is the world's largest public funder of medical research, and NCI is the nation's leading federal agency dedicated to cancer research and training. Together, their investments support researchers and sustain the clinical trial networks, data systems, cancer centers, and training programs needed to translate scientific discoveries into advances for patients.

What sustained federal investment makes possible is not abstract. For decades, researchers considered KRAS, a cancer-driving protein involved in many pancreatic, lung, and colorectal cancers, among the most difficult targets in cancer biology (see **Basic Research Decoding Cancer's Complexities**, p. 34). Long-term NIH-supported research helped build the scientific foundation needed to understand *KRAS*-driven cancers and pursue therapeutic approaches that once seemed impossible. In 2026, promising clinical data showed that an experimental KRAS-targeted therapy substantially extended survival for patients with metastatic pancreatic cancer whose disease had progressed after chemotherapy. This advance is not a cure, but for patients and families facing one of the deadliest cancers, it represents more time, more options, and more hope while science drives forward.

THE HONORABLE
Mark DeSaulnier

US Representative for California's 10th District

"At the time of my cancer diagnosis in 2015, my doctor told me that 15 years prior, a similar diagnosis would have been a death sentence. The fact that over 10 years later I continue to serve as a member of Congress, live my life to the fullest, and treat my cancer with a small pill I take daily, is the direct result of the transformational federal investments in medical research that have saved millions of American lives and improved quality of life for countless others.

"My personal experience with cancer, which I got just after coming to Congress, opened my eyes to the important role the federal government has in supporting patients. Experiencing firsthand the gaps in cancer care, the difficulty of navigating our health care system, and the value of scientific research, I co-founded the bipartisan Cancer Survivors Caucus and have introduced legislation to support cancer patients, survivors, and their families, and to advance medical breakthroughs when it comes to treating and curing this disease.

"Now, as scientific and medical research funding are under relentless attack from an Administration determined to slash crucial government funding across the board—human toll be damned—I am more determined than ever to fight for the investments that saved my life and the lives of so many others."

THE HONORABLE
Shelley Moore Capito

US Senator for West Virginia

"America has been, and must continue to be, a leader in biomedical research. As Chairman of the Labor-HHS Appropriations Subcommittee, this has been a top priority. One of the Senate Appropriations Committee's first hearings last year showcased biomedical researchers and how those living with cancer have benefited from the breakthroughs that have recently occurred. Their stories and accomplishments set the tone and resulted in the bipartisan support that led to the Committee's full support of the National Institutes of Health. Cancer has impacted all of us, affected our families, colleagues, and friends, regardless of where we are from or our political affiliation. I remain committed to advancing cancer research on a bipartisan basis and building on the success we've been able to foster."

Advances like these often begin years before they are visible to patients. They depend on laboratories, clinical studies, data systems, research infrastructure, and scientific talent that must be supported consistently over time. At a moment when cancer science is revealing new possibilities in immunotherapy, precision medicine, early detection, prevention, and data-driven discovery, stable federal investment is essential to ensure that promising ideas can move forward and reach the patients and families who are waiting.

In fiscal year (FY) 2026, Congress reaffirmed the nation's bipartisan commitment to medical research by rejecting proposed cuts to NIH and NCI and enacting appropriations that continued critical support for cancer research. The FY 2026 appropriations agreement provided modest increases for NIH and NCI, and included policies intended to promote stability across the research system, protect NIH research infrastructure, and restrict expanded use of multi-year funding mechanisms that could reduce the number of new research grants supported in a fiscal year. Leaders across the cancer research community took note. In February 2026, the Fellows of the AACR Academy expressed appreciation to congressional appropriators for prioritizing medical research and cancer science in FY 2026, emphasizing that fully delivering on the current scientific opportunities requires not only robust funding, but also a research environment that supports meritorious science and early-career investigators working to establish independent research careers.

The American public also recognizes the value of this investment. A national AACR survey conducted in August 2025 found overwhelming bipartisan support for federal funding for medical and cancer research, with 89 percent of voters favoring the use of taxpayer dollars to fund medical research, 83 percent supporting increased federal funding for cancer research, and 71 percent saying that increasing federal funding for medical research should be a top congressional priority. For patients and families, including policymakers like Representatives Mario Díaz-Balart (R-FL) and Mike Lawler (R-NY), federal funding reflects something deeply personal: It is a national commitment to improving health, saving lives, and giving people more time.

But public support, however broad, does not by itself sustain progress. Federal funds must be implemented as intended, awarded in a timely and predictable manner, and guided

by scientific merit. When appropriated funds are delayed, narrowed, or redirected in ways that limit the number of meritorious grants supported, the consequences are felt across laboratories, clinical studies, training programs, and ultimately by patients waiting for better options.

As of June 14, 2026, NIH competitive awards remained 36 percent below the FY 2021 to FY 2024 year-to-date average by number of awards and 27 percent below by award value. At NCI, competitive awards were 41 percent below the same year-to-date average by number of awards and 25 percent below by award value. These gaps will have profound consequences. Laboratories operate on grant cycles, hiring timelines, equipment needs, study protocols, and patient enrollment schedules that require stability. When awards are delayed or compressed late in the fiscal year, research teams are forced into uncertainty, studies may open later than planned, early-career scientists may lose critical support, and patients may face fewer opportunities to enroll in clinical trials.

Delays in awarding funds are one threat. The structure of grantmaking is another. Expanded use of multi-year, or forward funding has raised concerns within the scientific community because it can require NIH to commit more funding upfront to fewer grants, reducing the number of new and competing awards the agency can support in a single fiscal year. By May 15, 2026, NIH had used forward funding for 601 competitive research project grants totaling $402 million, which was far above the number and value of forward-funded competitive awards at the same point in FY 2024 and FY 2025. While forward funding may provide stability for individual awards, broad use of this mechanism can narrow the number of scientific ideas tested, investigators supported, and opportunities pursued. Progress against cancer depends on a steady flow of new ideas, new studies, and new investigators. When that flow slows, patients ultimately wait longer for the next breakthrough.

The rules governing federal research awards matter as well. The President's executive order on federal grantmaking and the White House Office of Management and Budget's proposed revisions to the federal grants framework have raised serious concerns about policies that could expand political discretion in research funding decisions, weaken merit-based review, create uncertainty around active awards, or restrict essential research costs and scientific collaboration. Federal research funding works best when awards are guided by scientific merit, expert review, transparency, and public health need. Protecting those principles is essential to sustaining the research system that has made the United States a global leader in medical research and cancer science.

The stakes extend beyond medical research. Federal support for medical research is one of the nation's most impactful investments in American innovation and economic strength. As outlined by **Representative Mike Levin (D-CA)** (see p. 182), NIH-supported research sustains jobs, supports local economies, drives small business innovation, strengthens

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THE HONORABLE
Mario Díaz-Balart
US Representative for Florida's 26th District

"As a senior member of the House Appropriations Committee, I have witnessed firsthand the lifesaving impact that responsible federal investment in cancer research delivers to our communities. The sustained federal funding towards cancer research that I have supported has helped drive remarkable progress, ensuring that the United States remains at the forefront of medical innovation while bringing us closer to a future where fewer families are devastated by the disease.

"Today, virtually every American has been affected by cancer in some way. Whether through the diagnosis of a family member, a close friend, or their own experience with the illness, cancer has left an indelible mark on families and communities across the nation. Unfortunately, my family is no exception.

"Since my days serving in the Florida State Legislature, where I worked to secure the University of Miami's National Cancer Institute (NCI) designation, to my time in Congress, I have believed in NCI's mission to advance lifesaving research and accelerate innovation. The importance of federal and academic collaboration in cancer research cannot be overstated.

"In just the last two fiscal years, Florida International University received critical congressional support, through the appropriations process, that allowed them to expand upon their groundbreaking development of functional precision drug testing for treatment-resistant cancers. Likewise, centers such as the Moffitt Cancer Center, renowned for its preeminence in cancer treatment, have remained a recipient of federal support, due to their excellence in cancer screening and early detection in underserved communities.

"While cancer remains a devastating disease, the advances we have made through innovative research give me hope and inspire me to remain steadfast in supporting these lifesaving efforts."

THE HONORABLE

Mike Levin

US REPRESENTATIVE FOR CALIFORNIA'S 49TH DISTRICT

You have long been one of Congress's strongest voices for biomedical research. What first drew you to championing federal investment in cancer research, and why has it remained a priority for you?

The region that I represent is home to some of the nation's leading cancer research institutions, which rely on federal funding to conduct critical research and provide lifesaving treatment. Many individuals in our district need access to the most advanced care, and these institutions are at the forefront of providing essential cancer treatments. Many cancer and biomedical research institutions are facing drastic federal funding cuts, so it is more important than ever to defend their ability to conduct research and provide lifesaving care. As a member of the House Appropriations Committee, I am fighting these cuts and working instead to increase federal investments in these programs and resources.

Constituent Andrew Schorr, a two-time cancer survivor, credits a clinical trial funded by the National Institutes of Health (NIH) with saving his life. What have stories like his taught you about what federal investment in cancer research means for patients and families?

Andrew Schorr is a perfect example of how federally funded cancer research can truly mean the difference between life and death. Andrew was diagnosed with blood cancer twice, and in each instance, treatments powered by federal investments saved his life. We need sustained federal support for NIH so that every American battling cancer, including Andrew, has access to cutting-edge care when it matters most.

You championed billions in funding for NIH, including the Cancer Moonshot. Why is sustained funding for NIH and the National Cancer Institute (NCI) essential to continued progress against cancer?

When NIH funding falters, cancer research suffers. It's as simple as that. That's why I fought for language included in the fiscal year 2026 appropriations bill that prohibits this Administration from capping reimbursements for research institutions. Our research institutions need consistent support so that they can focus on making innovative strides in cancer prevention, diagnosis, and treatment, rather than worrying whether they'll be able to afford the talent or resources they need.

Why is stable, predictable research funding important, and what role should Congress play in protecting it?

Stable funding is essential to progress. Without skilled researchers and multi-year trials, we cannot achieve breakthroughs in the field. Congress is responsible for passing funding bills before the end of the fiscal year. Unfortunately, due to the gridlock in Washington, that doesn't always happen. I am the only Member from San Diego and Orange Counties on the House Appropriations Committee, where I fight for the timely passage of funding bills that impact cancer research, clinical trials, and other critical programs. I prioritize working with members on both sides of the aisle to get this done and ensure NIH receives funding yearly. I am acutely aware that any delays or lapses in funding in cancer research are not minor issues—these delays and lapses can have detrimental effects on breakthrough research for years down the line.

The 49th District sits within one of the nation's leading life sciences regions. How do you see federal research investment shaping both the health of your constituents and the innovation economy of San Diego and North County?

Life sciences are a pillar of this region. Three out of California's 10 NCI-designated cancer centers are right here in San Diego. The San Diego region at large has over 2,000 companies and over 100,000 jobs in the life sciences sector. Supported by federal funding, these companies and careers can continue to thrive and grow, maintaining our region's stature as one of the leading hubs of innovation in both the United States and the world. When we produce these innovations, constituents can receive the most advanced care modern medicine has to offer.

What is your message to the scientists, physicians, and researchers working every day to make progress against cancer?

Thank you for your incredible work. You are actively saving or improving the lives of millions of people, and our country is better off because of it. I will continue to fight alongside you to find a cure for cancer and to ensure you get the resources you need to get the job done.

universities and medical centers, and helps maintain US leadership globally in medical science. In FY 2025 alone, NIH-supported research generated more than $94 billion in economic activity and supported nearly 391,000 jobs nationwide, with every $1 invested in NIH research generating approximately $2.57 in economic activity. That leadership is not self-sustaining. As other nations increase their own investments in medical research, the United States cannot assume that its current leadership status will endure without continued significant investment in meritorious medical research.

In FY 2027, the President's budget again proposed significant reductions to NIH funding as well as additional policy changes that would weaken the nation's research capacity and potential. If enacted, these reductions would make it harder for NIH and NCI to support investigator-initiated science, pursue targeted funding opportunities, invest in new investigators, test highly promising ideas, and sustain the discoveries that patients are counting on. At a time when cancer science is advancing rapidly, reducing federal support or destabilizing federal grantmaking would slow progress, weaken US leadership in biomedical innovation, and delay breakthroughs that patients and families are waiting for.

For patients and families, federal research investments are measured in time: time for a clinical trial to open, time for promising therapy to advance, time for a young investigator to pursue a new idea, and time for science to deliver new hope. Continued progress against cancer depends on the choices policymakers make now. With sustained investment in medical research, timely implementation, merit-based review, and continued bipartisan leadership, the United States can protect the future of cancer research and ensure that the next generation of breakthroughs reaches the people who need them.

THE HONORABLE
Mike Lawler

US Representative for New York's 17th District

"The fight against cancer is one of the most important investments we can make in the health and future of our country. By supporting lifesaving research, expanding access to early detection, and encouraging medical innovation, we can continue making real progress for patients and families while bringing us closer to a world where more cancers are prevented, detected early, and cured."

Investing in the People Who Drive Cancer Research and Care

The remarkable progress against cancer achieved over the past several decades has been made possible by the scientists, clinicians, trainees, and research staff whose collective talent and effort have fueled discoveries and translated them into better outcomes for patients. Sustaining and accelerating that progress will require a cancer research and care workforce that is sufficient in number, highly skilled, and supported at every stage of the career pathway. As described by **Representative James Walkinshaw (D-VA)** (see p. 184), building and sustaining this workforce is essential to ensuring that advances in cancer research and patient care continue for decades to come.

A robust workforce is also one that draws on the full breadth of the nation's talent. Recruiting, training, and retaining individuals from across communities, backgrounds, and life experiences expands the pool of people contributing to cancer research and helps ensure that the enterprise can meet the needs of all patients. A diverse workforce that brings together individuals with varied perspectives and educational backgrounds is more likely to ask innovative scientific questions, develop more relevant study designs, and adopt varied approaches to data collection and interpretation, ultimately expanding the scope of scientific knowledge (1048). A workforce that fails to develop talent from large segments of the population cannot reach its full size, strength, and potential.

Federal training and career-development programs play an important role in building this workforce. Decades of federal investment in these programs have helped broaden participation in the medical research workforce. Participation in two long-standing NIH undergraduate training programs—the Research Initiative for Scientific Enhancement program and the Minority Access to Research Careers program—more than doubled the rate of doctoral degree completion in the biomedical sciences among students from underrepresented backgrounds (1049). Sustained investment in these programs strengthens the research workforce and, in turn, the pace of progress against cancer.

Protecting and strengthening the cancer research and care workforce through sustained federal investment in research, training, and career development are essential to ensuring that progress against cancer continues for patients everywhere.

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THE HONORABLE

James Walkinshaw

US REPRESENTATIVE FOR VIRGINIA'S 11TH DISTRICT

You served alongside Congressman Gerald (Gerry) E. Connolly for many years before succeeding him. How has his fight with cancer, and his example, shaped your commitment to this issue?

Congressman Connolly taught me that public service is about turning even your hardest moments into opportunities to help other people. I had the privilege of serving as Gerry's Chief of Staff for more than a decade, and even after his diagnosis, he never stopped fighting for his constituents or looking for ways to improve people's lives.

Helping carry the Gerald E. Connolly Esophageal Cancer Awareness Act, his final bill, across the finish line was deeply personal for me. Gerry understood that early detection can save lives, and he wanted future patients and families to benefit from greater awareness and better screening. The legislation directs the Government Accountability Office to examine esophageal cancer screening and care under the Federal Employees Health Benefits Program, turning Gerry's personal battle into lasting public policy.

His example reinforced something I have always believed: Our responsibility in public office is to leave things better than we found them. When families face a cancer diagnosis, Congress should do everything possible to support research, improve early detection, and remove barriers to care.

How has that experience informed your view of why federal investment in cancer screening, prevention, and research matters?

Cancer touches nearly every family in America. It reminds us that public policy is not abstract. It is deeply personal. Federal investment in prevention, screening, and research has transformed what was once impossible into everyday medical practice. Patients are living longer because of decades of research supported by institutions like the National Institutes of Health (NIH) and the National Cancer Institute (NCI). Early detection saves lives, improves outcomes, and often reduces the long-term cost of treatment.

I believe the government has an important role in supporting scientific research and making breakthroughs. When we invest in biomedical research, we invest in hope for patients waiting for a breakthrough, families searching for answers, and future generations who deserve better treatment options. That is why I supported full funding for NIH and the National Science Foundation.

Why is protecting and supporting the federal scientific workforce essential to the fight against cancer?

Northern Virginia is home to thousands of dedicated public servants, including scientists, physicians, and researchers whose work improves lives across the country. When people talk about NIH, NCI, or the US Food and Drug Administration, they often think about institutions. I think about the people. They are the researchers designing clinical trials, reviewers evaluating promising therapies, scientists advancing our understanding of cancer biology, and public servants moving discoveries from the laboratory to patients. For many of them, their work is a lifelong commitment to the cause. These professionals are the reason progress happens. Undermining the federal scientific workforce means slowing research, delaying innovation, and ultimately delaying hope for patients and families.

What is your message to the scientists, physicians, and researchers working every day to make progress against cancer?

Thank you. Thank you for choosing careers dedicated to serving others. Thank you for the long hours in laboratories, hospitals, and clinics. Thank you for every clinical trial, research paper, difficult diagnosis delivered with compassion, and breakthrough that gives patients another chance. Progress against cancer has never happened by accident. It has happened because generations of scientists, physicians, nurses, researchers, and public servants refused to stop searching for better answers.

Applying Regulatory Science to Ensure Safe and Effective Cancer Therapies

The US Food and Drug Administration (FDA) works to protect the public health by ensuring the safety and efficacy of products that together account for about 20 percent of the US economy, including medical devices, tobacco products, and drugs (1050). This work includes authorities across various stages of the cancer drug development process, ranging from translational laboratory studies to clinical trials and post-marketing evaluation.

As our understanding of cancer has advanced, cancer drug development has become increasingly complex. To better integrate the various disciplines required to understand cancer therapeutics, the FDA Oncology Center of Excellence (OCE) was established in 2017. This initiative brought together experts from across major FDA medical product centers, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health, in service of streamlining oncology drug regulation. Since 2023, OCE has overseen nearly 200 approvals for cancer therapies, with over 50 approvals in 2025 alone. This is despite the significant turnover the agency has faced, particularly in OCE, where a staff of around 100 clinical reviewers, responsible for evaluating medical research and clinical trials data to determine whether the benefit–risk ratio for a given cancer therapeutic could support approval, was reported to have reached only half that size (1051). These significant departures among career staff are matched by that of senior leadership, for which there have been 13 center directors across CDER and CBER between 2025 and 2026 (1052).

Still, the agency has managed to push forward a variety of new policies and positions that clarify how oncology drug developers can advance the safety and efficacy of therapeutics while maintaining the rapid pace of innovation. The FDA *2025 OCE Annual Report* highlights significant achievements including 70 approvals, 1277 meetings with sponsors, 9 guidance documents, and 33 workshops or events (1053).

Advances in Rigorous Clinical Trial Design

Clinical trial design continues to evolve to generate more rigorous, efficient, and patient-centered evidence that informs both regulatory decision-making and clinical practice. Recent advances have focused on incorporating the patient perspectives into drug development, optimizing dose selection to enhance patient outcomes, modernizing approaches to evaluating complex combination therapies, and streamlining trial conduct while maintaining scientific rigor. These efforts are helping ensure that oncology clinical trials produce evidence that is both scientifically robust and meaningful to patients.

Patients are increasingly recognized as essential partners in the design and evaluation of cancer clinical trials. Through the Patient-Focused Drug Development (PFDD) initiative, FDA continues to advance approaches for systematically incorporating patients' experiences, preferences, symptoms, and treatment priorities into medical product development. FDA's PFDD Guidance Series provides recommendations for collecting patient experience data and selecting, developing, or modifying fit-for-purpose clinical outcome assessments (COAs) that measure outcomes most meaningful to patients (1054). These efforts were highlighted during the 10th Annual Clinical Outcome Assessment in Cancer Clinical Trials Workshop, held in October 2025, which convened regulators, researchers, patient advocates, and industry representatives to discuss advances in integrating patient reported outcomes and other COAs into oncology drug development (1055). As patients receive increasingly personalized therapies and remain on treatment for extended periods, incorporating the patient voice has become essential for understanding treatment benefit beyond traditional clinical endpoints such as tumor response and survival (1056).

Clinical trial design is also evolving to optimize dose selection throughout drug development. Historically, many oncology therapies were developed using the maximum tolerated dose paradigm, but recent regulatory efforts have emphasized identifying doses that maximize clinical benefit while minimizing treatment-related toxicity. FDA continues to encourage sponsors to incorporate model-informed drug development strategies, including quantitative systems pharmacology (QSP), to support scientifically informed dose selection during early clinical development. In 2025, FDA released draft guidance describing the use of QSP-based approaches to determine the minimum anticipated biological effect level for first-in-human clinical trials (1057). Additional draft guidance addressing dosage optimization for oncology therapeutic radiopharmaceuticals further encourages sponsors to evaluate dose-response relationships early in clinical development (1058). Reinforcing these principles, discussions during the July 17, 2025, meeting of FDA's Oncologic Drugs Advisory Committee (ODAC) in which the biologics license application for belantamab mafodotin-blmf (Blenrep) was reviewed, highlighted the importance of identifying doses that optimize efficacy while minimizing treatment-related toxicity (see **Increasing Access to and Representation in Clinical Trials**, p. 186).

As oncology treatment increasingly relies on combination therapies, clinical trial designs are being leveraged to address the unique scientific and regulatory challenges of evaluating multi-agent regimens. FDA guidance on the development

of cancer drugs for use in novel combinations provides recommendations for demonstrating the contribution of each individual therapy to the overall treatment effect while maintaining scientifically rigorous and feasible study designs (1059). Ongoing efforts across the oncology research community continue to refine approaches to evaluating combination therapies, including innovative trial designs, biomarker-driven strategies, and statistical methods that improve the efficiency of clinical development while maintaining rigorous standards for demonstrating safety and effectiveness (1060,1061). These advances are helping accelerate the development of combination regimens while preserving the scientific integrity needed to support regulatory decision-making.

Increasing Access to and Representation in Clinical Trials

Historically, clinical trial cohorts have differed significantly from real-world patient populations in key demographic characteristics, such as age, comorbidities, race, ethnicity, and geographic location. These differences can limit the generalizability of trial findings and contribute to disparities in access to innovative cancer therapies (1062). To ensure the quality and relevance of clinical cancer research going forward, it is essential for trials to have representative cohorts that mirror the patient populations most likely to benefit from newly approved therapies.

Recent analyses indicate measurable progress in aligning clinical trial populations with real-world demographics. A 2025 study reported that the age gap between patients enrolled in oncology registrational trials and the general population has narrowed over time (1063). These findings likely reflect sustained collaborative work between regulators, academia, patient advocacy organizations, and industry to modernize eligibility criteria and reduce unnecessary exclusions while maintaining patient safety.

In December 2025, FDA finalized its guidance titled *Enhancing Participation in Clinical Trials—Eligibility Criteria, Enrollment Practices, and Trial Designs* (1064), building on previous efforts to improve trial representativeness. This guidance encourages sponsors to adopt scientifically justified eligibility criteria, reduce unnecessary exclusions, incorporate patient-centered trial designs that are flexible and accessible, and implement enrollment practices that facilitate participation among populations historically underrepresented in clinical research. These recommendations aim to generate evidence that more accurately reflects patients treated in routine oncology practice and reinforce FDA's commitment to enhancing clinical trial representation.

FDA has also continued to emphasize the importance of ensuring that data supporting regulatory decisions are applicable to US patients. As noted earlier, during the July 17, 2025, meeting of ODAC, committee members discussed the biologics license application for belantamab mafodotin-blmf and considered, among other issues, whether the study population adequately reflected patients likely to receive the therapy in the United States (1065). Advisory committee members noted that two pivotal studies included limited enrollment of US patients and used comparator regimens that are not commonly administered in the United States, raising concerns about the generalizability of the findings to US clinical practice. Discussions during the meeting underscored that as oncology trials become increasingly global, study designs must continue to include appropriate control arms and adequate representation of US patients to ensure that trial results remain relevant for regulatory decision-making and the patients who will ultimately receive these therapies.

Oncology Registries: Strengthening Real-World Evidence

WHAT ARE ONCOLOGY REGISTRIES?

Recognizing the need for national cancer incidence data to support public health planning, Congress established the **National Program of Cancer Registries (NPCR)** in 1992. Today, oncology registries systematically collect information on patients with cancer, including demographics, diagnoses, treatments, and outcomes, to better understand how therapies perform in routine clinical practice.

WHY ARE THEY IMPORTANT?

High-quality oncology registries can:

- **Generate real-world evidence** that complements data from traditional clinical trials.
- **Improve understanding of treatment effectiveness and safety** across diverse patient populations.
- **Support regulatory decision-making** throughout the medical product life cycle.
- **Identify evidence gaps** and inform future clinical research.

Source: (1067). W68

Another important advance has been the continued integration of real-world evidence (RWE) into oncology drug development and regulatory decision-making. In December 2025, FDA announced actions intended to eliminate long-standing administrative barriers to incorporating RWE into reviews of drug and medical device applications (1066). These changes are expected to facilitate the use of data collected outside traditional clinical trials, including electronic health records, claims databases, and disease registries, to complement evidence generated through randomized studies, particularly for populations that have historically been underrepresented in clinical trials.

These regulatory, methodological, and policy advances reflect a broader transformation in oncology clinical research. By actualizing these practices, researchers and regulators are working toward a clinical trial ecosystem that is more efficient, more inclusive, and more representative of the patients who will ultimately benefit from new cancer therapies.

Rapidly Delivering Safe and Effective Therapies to Patients

Cancer drug development continues to deliver therapeutics that are more effective and less toxic than previous treatments. This year in particular, the drug development community has come together and made significant strides toward further increasing the rate of innovation to improve the availability of these transformative therapeutics and thereby improve outcomes for all.

FDA has led the charge on this, releasing a number of guidance documents, initiatives, and more with the potential to significantly speed drug development. FDA's flagship program to accelerate drug development, the Accelerated Approval Program, continues to allow the earlier approval of drugs that treat serious conditions, such as cancer, based on early endpoints of clinical benefit instead of traditional endpoints that may require more time to be evaluable. As of June 2026, over 180 oncology drugs are currently available under accelerated approval or have been converted from accelerated approval to traditional approvals, signaling their confirmed positive impacts for patients (1068). Indeed, a recent study showed patients gained over 50,000 life years as a result of drugs that received accelerated approval during the analysis period (531). However, approving therapies based on early endpoints does carry risks as well as benefits. If the early endpoint an approval is based on does not strongly correlate with long-term outcomes, patients may be exposed to therapies that are inefficacious, are no better than standard of care, or may even be toxic. To protect against this, FDA recently outlined updated expectations for the withdrawal of therapeutics for which observed benefits that led to accelerated approval are not realized with longer-term endpoints (1069).

FDA has also emphasized rigorous processes for the selection and development of endpoints across clinical trials, including traditional clinical benefit endpoints such as the gold standard of overall survival (OS) in addition to the earlier endpoints that accelerated approval relies upon. For example, FDA and AACR co-led a public workshop, titled Approach to Novel Oncology Endpoint Development (1070). This workshop highlighted methods that the cancer research community can use to work together to develop new endpoints that mediate faster approvals while maintaining patient safety. In support of this work was a guidance on the use of the recently FDA-endorsed novel endpoint minimal residual disease (MRD) in multiple myeloma (1071). Researchers also continue to make progress toward the validation of novel endpoints, with significant multi-stakeholder collaborations such as the Friends of Cancer Research ctMoniTR Project, which seeks to standardize, and eventually establish, the use of circulating tumor DNA as a potential early endpoint, reporting promising data and moving the field toward the prospective trials necessary to establish a novel endpoint (1072).

In addition to this focus on novel endpoints, regulatory science research continues to determine how to best leverage statistics and clinical trial designs in service of a better understanding of OS. FDA recently published a guidance discussing approaches to and considerations for evaluating OS (1073), and past efforts such as the FDA-AACR-ASA Workshop on Overall Survival in Oncology Clinical Trials from 2023 continues to bear fruit, with a special six-article series published by leaders of the workshop that provides updates and advances in the evaluation of OS (1074). Patient voices have also expressed the continued essentiality of OS in approval decisions, with a comprehensive survey of breast cancer patients identifying unified support for the idea that faster approval at the expense of certainty about the clinical benefit of a drug is most acceptable when no alternative treatments exist or when the therapeutic is expected to be transformational (1075).

Federal biomedical research agencies have also taken a broader interest in the development of novel approach methodologies (NAMs), which are innovative methods to assess the safety or efficacy of drugs and include human-based laboratory studies and computational models (see **Generating Knowledge Through Basic Research**, p. 31). By fostering the use of these models through their Roadmap to Reducing Animal Testing in Preclinical Safety Studies, FDA hopes to reduce not only animal testing but also the lag time between drug discovery and clinical trial initiation (1076). FDA has made significant progress toward this goal in oncology drug development by releasing guidance outlining general principles for the use of NAMs and guidance specific to the use of NAMs within

oncology drug development (94,1077). Of particular interest, the oncology specific guidance recommends instances in which traditional 3-month toxicity studies in non-human primates may be replaced with rodent studies or other evidence, potentially decreasing both development timelines and costs.

These programs synergize with an abundance of new efforts aimed directly at increasing the speed and ease of running clinical trials. Stakeholders across the research ecosystem are facing growing challenges in initiating and conducting studies efficiently, with operational barriers at both the trial and site levels such as protocol complexity, redundant startup processes, contracting, institutional review board review, and infrastructure limitations. Further, enrollment, maintaining equipoise throughout the trial, and in some cancers long timelines to trial completion can mean that even exceptional therapeutics experience difficult journeys from discovery to approval. This has led to many trials being primarily conducted in countries outside the United States, with China and Australia becoming home to a significant portion of clinical studies (1078,1079).

One issue that both impacts clinical trial availability for patients and extends development timelines is that trials traditionally close between phases to report data to regulatory agencies. FDA has released two specific efforts to address this. First, they released guidance on the use of Bayesian clinical trial designs (see **Sidebar 26**, p. 101), which can support the use of adaptive seamless trials that do not pause, as well as allow for the integration of data from outside the trial into final analyses, potentially spurring more efficient and well-informed trial analyses (1080). FDA is also working toward a pilot program for real-time clinical trials, which do not need to pause because they report safety data to FDA throughout the course of the trial (1081). Two clinical trials using this paradigm are already underway as test cases, both in early-phase oncology settings. Further, the US Department of Health and Human Services (HHS) announced an agency-wide initiative known as Operation TrialBlazer with the goal of strengthening US leadership in clinical research (1082). Under this initiative, FDA is planning a program that would accelerate trial initiation by expediting the investigational new drug process, which facilitates authorization for new drugs to be tested in human patients (1083).

Together, all of these initiatives bring together regulatory innovation and cancer science to provide cancer patients with access to new therapeutics as quickly and as safely as possible.

Regulatory Collaboration and Global Harmonization

Regulatory collaboration and global harmonization are essential pillars in accelerating the development and delivery of safe, effective cancer therapies worldwide. By aligning standards, processes, and scientific requirements across countries, regulatory harmonization facilitates faster access to new treatments, reduces inefficiencies, and helps ensure patients around the world benefit equally from biomedical innovation.

FDA has played a central role in these efforts, engaging with international stakeholders through several global organizations, including the International Council for Harmonisation (ICH), the International Pharmaceutical Regulators Programme, and the International Coalition of Medicines Regulatory Authorities (1084). For example, FDA has published multiple guidance documents recently prepared under the auspices of ICH, with topics ranging from clinical trial protocol standardization, computational model–informed drug development, and best practices for adaptive clinical trials (1085-1087). Additionally, FDA continues to extend its reach to new partners while also strengthening its relationship with long-time allies, as evidenced by its cooperative agreement with the recently formed African Medicines Agency and the establishment of a new program in partnership with the United Kingdom Medicines and Healthcare products Regulatory Agency, which installed on-site reciprocal liaisons at the respective agencies (1088,1089). Topic-specific collaborations have also been established, particularly with the European Medicines Agency and FDA aligning on 10 guiding principles for the use of artificial intelligence (AI) to advance drug and biological product development (1090).

FDA OCE has also established key relationships with international stakeholders through its flagship Project Orbis initiative, which is now in its seventh year. Through Project Orbis, FDA OCE established a structured pathway for collaborative evaluation of cancer therapies across international regulatory agencies, including those from Brazil, Israel, Singapore, Switzerland, the United Kingdom, Australia, and Canada, reducing delays and enabling more patients to benefit from lifesaving treatments sooner. In 2025, Project Orbis facilitated 19 product approvals, contributing to a total of 143 approvals through April 2026 (1091).

Regulatory collaboration has become a foundational element of the global oncology ecosystem, reflecting a sustained commitment to aligning regulatory science for faster and more equitable access to cancer therapies. However, more work remains to be done; a lack of harmonization has, in part, led to discrepancies in the availability of certain therapeutics throughout the world, including chimeric antigen receptor (CAR) T-cell therapy and other immunotherapies (1092,1093). The future of global cancer care will be shaped by the shared understanding, representation, and innovation that results from these important collaborations and those that are to come.

Advancing Policies to Strengthen Cancer Prevention and Screening Programs

Cancer prevention and early detection are among the most powerful tools for reducing cancer incidence and mortality. In fact, almost half of all cancer deaths globally could be avoided through primary prevention and improvements in early detection and screening (1094). In the United States, over 40 percent of yearly cancer deaths could be prevented because the cancer can be attributed to modifiable risk factors, such as tobacco use, dietary factors, and ultraviolet (UV) exposure (see **Reducing the Risk of Cancer Development**, p. 55). Research has shown that routine screening for common cancers and early warning signs using evidence-based approaches is essential for improving treatment options and survival (see **Cancer Screening for Early Detection**, p. 82). However, the benefits of prevention and screening are not shared equitably. Inequities in access to screenings and follow-up care contribute to health disparities and reduced survival in some patient populations. Persistent barriers, including cost-sharing, underinsurance, limited access to primary and specialty care, inadequate follow-up after abnormal findings, and geographic and structural inequities continue to delay diagnosis and worsen outcomes for many individuals, particularly those living in rural and medically underserved communities. Policymakers like **Senator Chuck Grassley (R-IA)** (see p. 190) are continuing to work to support these rural medical services, investing in programs such as the Rural Community Hospital Demonstration. To continue progress against cancer and improve survival rates, it is essential to implement innovative and inclusive cancer prevention and screening policies that ensure equitable access to early detection for all populations.

Policymakers and Congress have taken notable steps to modernize the prevention and screening landscape. The Nancy Gardner Sewell Medicare Multi-Cancer Early Detection (MCED) Screening Coverage Act was signed into law on February 3, 2026, as part of the Consolidated Appropriations Act funding federal agencies through the remainder of FY 2026 (1095). Introduced by **Senator Mike Crapo (R-ID)** (see p. 191), the legislation modernizes the Medicare program by creating a new benefit category for MCED tests, which will allow the Centers for Medicare and Medicaid Services (CMS) to initiate an evidence-based coverage process for such tests upon their approval by FDA. Beginning in 2028, Medicare will be authorized to cover and pay for MCED screening tests that are FDA-approved and used to screen across many cancer types, where CMS determines such coverage is appropriate. Increased access to coverage though CMS remains a priority for Congress, with Representative Doris Matsui (D-CA) and **Representative Gus Bilirakis (R-FL)** (see p. 192) introducing the Finn Sawyer Access to Cancer Screening Act in the 119th Congress, which would increase coverage of certain cancer diagnostic and laboratory tests. Although MCED tests are not a substitute for guideline-recommended organ-specific screening, the law represents a major policy milestone by establishing a mechanism for coverage of emerging blood-based technologies that may eventually complement existing screening programs and help identify cancers that currently lack recommended screening approaches. This policy advance holds tremendous promise for increasing the likelihood that treatment will be successful, lowering treatment costs, and improving quality of life for patients and caregivers.

The Screening for Communities to Receive Early and Equitable Needed Services (SCREENS) for Cancer Act is bipartisan legislation that seeks to reauthorize and strengthen the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) for FY 2026 through FY 2030 (1096,1097). The Trump Administration's FY 2026 budget proposal called for eliminating federal funding to many critical cancer prevention and control programs, including the NBCCEDP. The SCREENS for Cancer Act would provide more flexibility to NBCCEDP grantees, allowing for greater emphasis on implementing innovative, evidence-based interventions and aggressive outreach to underserved communities through media, peer educators, and patient navigators. However, both the US House of Representatives and Senate bills are still awaiting action by their respective committees. The Find It Early Act was reintroduced in November 2025 by Representatives Rosa DeLauro (D-CT) and Brian Fitzpatrick (R-PA) and would require all health insurance plans to cover screening and diagnostic breast imaging with no cost-sharing for patients (1098). The bill is specifically designed to address coverage gaps for women at elevated risk and is essential to ensuring that out-of-pocket costs no longer serve as a barrier to lifesaving early breast cancer detection.

Early detection remains a focal point for Congress, which passed legislation like the EARLY Act Reauthorization, increasing funds for education and prevention programs for young women. The Increasing Access to Lung Cancer Screening Act aims to significantly reduce barriers to lifesaving lung cancer screening for underserved populations (1099,1100). The bill mandates that Medicaid programs cover annual lung cancer screenings at no out-of-pocket cost for individuals recommended for screening under US Preventive Services Task Force (USPSTF) guidelines and requires that Medicaid managed care organizations provide this coverage without prior authorization. The bill would also eliminate prior authorization requirements for lung cancer screening under Medicare and private insurers, expand Medicaid coverage for tobacco cessation counseling and pharmacotherapy, and establish a $10 million lung cancer screening education and outreach campaign at HHS.

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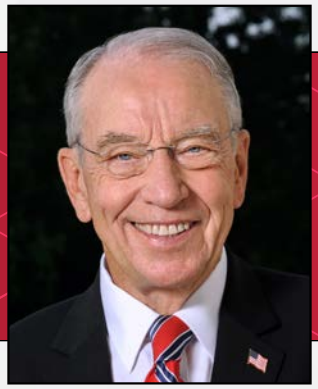


THE HONORABLE

Chuck Grassley

US SENATOR FOR IOWA

What are the most urgent gaps in rural cancer care, and what role should Congress play in closing them?

As with any public policy, the role of every lawmaker in Congress is to listen to constituents and grassroots advocacy groups to gather the facts and make informed decisions, including addressing gaps in cancer care. As a farm-state lawmaker, I bring a unique perspective to the policymaking table to advocate on behalf of families and health care providers living and working in rural communities. For example, I've prioritized keeping the doors of hometown hospitals, clinics, and pharmacies open through flexible federal funding measures, such as the Rural Community Hospital Demonstration and Rural Emergency Hospital programs, as well as enabling local pharmacists to be reimbursed for providing health care services.

I'm also working to address the gap in how patients access and navigate cancer screening recommendations. Too often, screening guidance is difficult to understand, changes over time, and is not readily integrated into the technology that patients and providers use every day. This can result in missed opportunities for early detection and treatment, particularly in rural communities where cancer mortality rates remain higher. By making screening information more accessible, timely, and patient-centered, the federal government can help reduce barriers to early detection and improve cancer outcomes. I want to enable more apps and web tools to get cancer screening information to patients and providers similar to the Decision Precision+ and Cancer Screen Iowa tools.

How have personal experience and the stories of patients and families shaped your efforts to expand early detection and remove barriers to cancer care?

Since my first term in the US Senate, my committee assignments have enabled me to roll up my sleeves at the policymaking table and shape federal policies on behalf of American families to improve delivery of care and health outcomes, from the "Katie Beckett waiver" to the Family Opportunity Act to the Accelerating Kids' Access to Care Act (AKACA). That work includes raising public awareness and expanding access to early screening and detection. My wife Barbara is a 39-year breast cancer survivor and credits early detection and surgery with saving her life. The enactment of the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act in February marked an important step forward. It will help clear the way to revolutionize cancer detection and expand Medicare coverage for lifesaving cancer screenings. Thanks to remarkable strides in research, therapeutics, and oncology treatments, many cancer diagnoses are no longer considered a death sentence. Just consider the recent promising breakthrough therapy for pancreatic cancer, for example.

Congressional oversight is critical to ensuring public health care programs and federal agencies efficiently and effectively serve the American people. Those efforts include improving care and outcomes for pediatric cancer patients. With the support of grassroots-led advocacy organizations, I spearheaded the bipartisan AKACA through the Senate to help kids kick cancer to the curb and live long, healthy lives. Representative government is a two-way street. I heard directly from families, patient advocates, and providers about how red tape prevented children with complex medical needs from receiving timely care or participating in an out-of-state clinical trial. More than half of these children are covered by Medicaid or the Children's Health Insurance Program, but state-by-state provider enrollment requirements created barriers to care outside their home states. State lines shouldn't dictate whether a child in the United States receives timely, lifesaving care. With AKACA on the books, specialty pediatric providers can enroll in multiple state Medicaid programs, giving families much-needed peace of mind. Moms and dads have enough on their plates to manage without dealing with cumbersome, bureaucratic red tape that delays care for their sick child. I'll continue my oversight work to ensure these laws work as Congress intended.

THE HONORABLE

Mike Crapo

US SENATOR FOR IDAHO

How has your experience as a prostate cancer survivor informed your approach to health policy, and your conviction that federal investment in cancer research, screening, and prevention saves lives?

Since coming to Capitol Hill, I have made combating cancer a top legislative priority. Losing a loved one to cancer, seeing others go through treatment, and going through treatment make the search for leading-edge treatment acutely personal. Thanks in part to sustained federal investments in research and care, we have seen remarkable progress in the past few decades, with game-changing improvements in screening, prevention, diagnostics, and treatments. As we continue that work, detecting more cancers at earlier stages will prove especially crucial.

This year, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection (MCED) Screening Coverage Act—legislation you championed for multiple Congresses—was signed into law, establishing a Medicare coverage pathway for multi-cancer early detection tests. What did reaching that milestone mean to you, and what impact do you hope it will have for patients, particularly seniors and those in rural states like Idaho?

Enactment of the MCED Screening Coverage Act is incredibly gratifying. Before, Medicare only covered preventive services explicitly authorized by Congress or recommended by the US Preventive Services Task Force. This meant many routine cancer screenings were not reimbursed, even though early detection of cancer is crucial in maximizing patient outcomes. According to the Idaho Medical Association, before passage, approximately 70 percent of cancer deaths were caused by cancers for which there were no covered screening tests. The MCED Screening Coverage Act establishes a pathway for Medicare coverage of MCED screenings once they are approved by the US Food and Drug Administration, rather than waiting for a lengthy additional legislative or regulatory approval process, making these important tests accessible to many more patients.

While enactment of the MCED Screening Coverage Act provides significant progress in multi-cancer screening, what else are you working on to improve cancer care?

I am co-leading bipartisan legislation with Senator Amy Klobuchar (D-MN) that would reauthorize the Breast Cancer Education and Awareness Requires Learning Young (EARLY) Act through 2031. The current authorization, which I helped secure in the fiscal year 2021 government funding package, is set to expire this year. In June, the Senate Health, Education, Labor and Pensions Committee advanced the legislation, which would ensure the Centers for Disease Control and Prevention continues campaigns to raise awareness of breast cancer risks among young women and encourage preventive care and early screening when appropriate. The law also supports research activities related to breast cancer prevention and educational efforts for physicians and other health care professionals involved in detecting and treating the disease. This legislation, like the MCED Screening Coverage Act, is part of my ongoing effort to align federal programs with preventive health goals aimed at reducing government expenditures on care and fostering a healthier nation.

MCED tests hold particular promise for identifying cancers that currently have no recommended screening test. Why is it so important to build coverage pathways for these emerging technologies, even as they continue to complement existing, guideline-recommended screening?

Cancer does not wait for regulatory processes and guidelines to catch up to it. Increasing access to proven screening tools will ensure many patients discover cancer when it is often most treatable. That holds tremendous promise for improving survival rates and driving down costs for patients, medical providers, and Medicare itself.

What is your message to the scientists, physicians, and researchers working every day to make progress against cancer?

Thank you. Scientific advancements have dramatically improved the country's capabilities to treat cancer, among many other health care concerns. The scientists, physicians, and researchers who work patiently to test hypotheses and evaluate treatments, often starting over time and again in search of microscopic answers that carry enormous importance, are profoundly commendable. Your commitment, knowledge, curiosity, and drive save lives and fuel our country's progress in the fight against cancer.

THE HONORABLE

Gus Bilirakis

US REPRESENTATIVE FOR FLORIDA'S 12TH DISTRICT

What are the most urgent gaps in rural cancer care, and what role should Congress play in closing them?

Despite tremendous advances in cancer treatment, too many patients still face barriers to timely diagnosis, innovative therapies, and affordable care. Delays in access to biomarker and genomic testing can prevent patients from receiving the most effective, personalized treatments. Many patients also continue to face high out-of-pocket costs for lifesaving medications, while cancer survivors often struggle with long-term health challenges, financial burdens, and gaps in follow-up care. My constituents have benefited tremendously from the continued expansion of the Moffitt Cancer Center, one of our nation's premier cancer treatment and research institutions. The lifesaving work taking place there is nothing short of extraordinary. Moffitt is setting the standard for precision medicine, pioneering breakthrough therapies, and giving hope to patients and families facing some of life's most difficult challenges. Seeing these innovations firsthand reinforces why we must continue investing in research and ensuring patients have access to the latest medical advancements. Congress has an essential role to play in closing these gaps. We must continue supporting robust funding for the National Institutes of Health (NIH) and the National Cancer Institute (NCI), while advancing policies that accelerate medical innovation, remove barriers to care, and ensure every patient has access to cutting-edge diagnostics and treatments regardless of where they live. We also have a responsibility to strengthen survivorship programs, reduce the financial burden of cancer care, and improve coordination across our health care system so patients receive comprehensive support long after treatment ends. Ultimately, our goal should be to ensure that every American has access to the right treatment at the right time while continuing to fuel the research that will lead to tomorrow's cures.

Why must progress against cancer remain a bipartisan priority?

Cancer does not discriminate based on political affiliation, geography, or background. Nearly every American family has been touched by this disease in some way, making the fight against cancer one of the few issues that consistently brings Republicans and Democrats together.

Investments in cancer research have led to groundbreaking discoveries that have saved millions of lives and improved quality of life for patients across the country. Supporting research, expanding access to innovative treatments, and improving survivorship are goals everyone can rally behind because they strengthen families, reduce health care costs over the long term, and give patients hope. This is an area where Congress has repeatedly demonstrated that bipartisan cooperation can produce meaningful results.

How have you worked to serve the cancer community?

I have worked to support cancer patients, survivors, caregivers, and the researchers working to find tomorrow's cures. Throughout my time in Congress, I have consistently supported increased federal investment in cancer research while advancing legislation that improves access to cutting-edge care.

One of my key priorities is the Finn Sawyer Access to Cancer Testing Act, bipartisan legislation that would expand patient access to comprehensive biomarker diagnostic testing. These advanced diagnostic tests help physicians identify the most effective treatments for each individual patient, allowing for more personalized care while avoiding unnecessary or ineffective therapies. I have also been a leading advocate for the Cancer Drug Parity Act, which would ensure patients pay the same out-of-pocket costs for orally administered cancer medications as they do for traditional intravenous treatments. As cancer care continues to shift toward innovative oral therapies, this legislation would help eliminate financial barriers that may otherwise prevent patients from accessing the treatment their physician recommends. Beyond legislation, I regularly work with patients, advocacy organizations, health care providers, and researchers to identify gaps in care, support medical innovation, and ensure federal policies keep pace with advances in cancer treatment. My goal is simple: Every patient should have timely access to the best available care while continuing to accelerate research that brings us closer to preventing and curing cancer.

THE HONORABLE
Tina Smith
US Senator for Minnesota

"Many of us have a deeply personal connection to cancer. For me, that's Minnesota Congressman Rick Nolan's daughter, Katherine. She died of lung cancer at the age of 46, and it turns out she's part of a devastating trend. Unlike every other demographic, lung cancer diagnoses in women who don't have traditional risk factors are actually increasing, and for many women, that diagnosis comes too late. This is why I wanted to work with organizations like the American Association for Cancer Research and with my colleagues across the aisle to promote research and prevention efforts.

"This collaboration is how we introduced and eventually passed the Women and Lung Cancer Research and Preventive Services Act in the US Senate. This lifesaving bill directs a review of current research on women and lung cancer, and how women can access lung cancer detection and preventive services. Your voices are powerful, and we need to keep up the fight against this devastating disease to improve awareness, early detection, research, and treatment options, especially for women like Katherine."

A significant barrier to cancer prevention and screening services is the associated cost and lack of insurance coverage for many individuals. Recent changes to federal health insurance policy threaten to further undermine access to cancer prevention and screening services. The Patient Protection and Affordable Care Act (ACA) requires most private health plans and Medicaid expansion programs to cover USPSTF-recommended preventive services, including evidence-based cancer screenings, without patient cost-sharing (1101). However, the expiration of the enhanced ACA Marketplace premium tax credits at the end of 2025 is expected to substantially increase premiums and reduce insurance coverage for millions of Americans (1102). The Congressional Budget Office estimates that will increase the number of uninsured people by approximately 2.2 million in 2026, and by an average of 3.8 million each year through 2034 (1103). In addition, the 2025 Federal Budget Reconciliation Law includes new Medicaid work requirements beginning in 2027 that are projected to further increase the number of uninsured individuals (1104,1105). Uninsured adults are significantly less likely to receive recommended cancer screening services and are more likely to be diagnosed with cancer at later stages, and these coverage losses threaten to erode recent progress in early detection and cancer outcomes. Sustaining affordable health insurance coverage is therefore essential to ensuring equitable access to evidence-based cancer prevention and screening services.

Improving Screening Guidelines and Risk-based Approaches

Cancer screening policy is developed through rigorous evidence review to maximize the benefits of early detection while minimizing potential harm, such as overdiagnosis, false-positive results, unnecessary procedures, and patient anxiety. USPSTF plays a central role in providing recommendations that inform insurance coverage of preventive services without patient cost-sharing under the ACA. Consequently, timely USPSTF review and updating of cancer screening recommendations are essential not only for ensuring that clinical practice reflects the latest evidence, but also for determining whether patients can access recommended screening without financial barriers. USPSTF issued a draft update to cervical cancer screening recommendations in December 2024 that would incorporate patient-collected high-risk human papillomavirus (hrHPV) testing as an option for some individuals ages 30 to 65, reflecting growing evidence that self-collection can improve access to screening while maintaining clinical accuracy (1106). However, USPSTF has not met since March 2025 after repeated meeting cancellations and postponements, and this draft recommendation has not been finalized (1107). Furthermore, in May 2026, the HHS secretary removed the USPSTF chair and vice chair, raising concerns about the panel's independence and potential for further delays in updating recommendations that shape cancer screening coverage and clinical care (1108).

Beyond USPSTF, there have been other important advances in cervical cancer screening policy. On January 5, 2026, the Health Resources and Services Administration (HRSA) announced landmark revisions to cervical cancer screening guidelines (1109). Approximately one in four women in the United States is not up to date on cervical cancer screening, a decline driven in part by the invasive nature of traditional Pap tests administered by a clinician (1110). The updated guidelines directly address these gaps and now recommend hrHPV testing every 5 years as the preferred screening method for average-risk women ages 30 to 65. Of crucial importance, women may now self-collect samples either in a clinical setting or at home, as clinical evidence has shown that self-collection is as effective as clinician collection and improves overall screening rates (1111). For women ages 21 to 29, Pap testing every 3 years remains the recommended approach. It is noteworthy that the revised guidelines also will require private insurers to cover not only the initial screening, but also all necessary follow-up diagnostic steps without cost-sharing,

effective January 1, 2027, thus closing a gap that had long exposed patients to unexpected out-of-pocket costs. The policy builds on FDA's 2024 authorization of self-collected hrHPV testing kits for use in health care settings and its May 2025 approval of the first at-home self-collection device (1112,1113). By expanding patient choice, reducing logistical and financial barriers, and extending access to underserved and rural populations, HRSA's updated guidelines mark a major advance for cervical cancer prevention and women's health nationwide. Together, these developments illustrate how evidence-based policy can accelerate the translation of scientific innovation into more accessible, patient-centered cancer prevention and screening strategies.

Currently, eligibility for population-based cancer screening programs is primarily based on age and biological sex. Recent research has underscored the limitations of such one-size-fits-all screening criteria and the need for more individualized, risk-based approaches. Personalized risk-based screening (PRBS) for cancer is an emerging approach that considers individual risk factors such as genetics, environmental exposures, family history, and health behaviors to tailor screening schedules. PRBS has shown promise for improving accessibility, increasing efficiency, and reducing health care costs of traditional screening programs. The WISDOM (Women Informed to Screen Depending on Measures of Risk) randomized clinical trial, which enrolled more than 46,000 women across the United States, demonstrated that personalized risk-based breast cancer screening tailored according to genetic testing, polygenic risk scores, and imaging-based risk scores was as accurate as annual mammography over 5 years and was associated with reduced unnecessary biopsies (501).

A complementary modeling study found that risk-stratified screening approaches based on a woman's 5-year absolute breast cancer risk would avert more breast cancer deaths and reduce false positives compared to standard age-based screening (502). Reflecting this evidence, the National Comprehensive Cancer Network's (NCCN) *Clinical Practice Guidelines: Breast Cancer Screening and Diagnosis* now include image-based AI risk assessment as an option starting at age 35 (1114). The guidelines establish an AI-determined 5-year risk threshold of ≥1.7 percent to classify an individual as being at increased risk. For patients meeting this threshold, NCCN recommends personalized risk-reduction strategies and supplemental imaging, such as breast magnetic resonance imaging or ultrasound, to optimize early detection.

Significant advances have also been made for lung cancer screening. Only approximately 1 in 5 eligible individuals in the United States underwent lung cancer screening in 2024, and analysis shows that increasing screening uptake to 100 percent could increase deaths prevented and life-years gained three-fold (442). Efforts to increase uptake include improving awareness of screening recommendations, broadening access to care, and targeting populations for which lung cancer screening will maximize life-years gained. Current USPSTF eligibility criteria for low-dose computed tomography (LDCT) lung cancer screening relies solely on age and smoking history, but a growing body of evidence supports the benefits of multivariable risk prediction models. A study of the comprehensive PLCOm2012 risk prediction model, which incorporates age, smoking history, education, body mass index, history of chronic obstructive pulmonary disease, prior cancer, and family history of lung cancer, found it detects more cases and is more efficient than screening based on traditional, categorical criteria (503). These findings reinforce earlier evidence that risk model-based eligibility for LDCT screening detects more lung cancers, particularly among women and underrepresented racial and ethnic minority groups, than categorical criteria alone and strengthens the case for moving toward model-based screening policies. Further development and integration of AI-based tools will better enable PRBS, empower more accurate cancer risk stratification, and shift patients from population-based to targeted screening. Implementation strategies and policies that address barriers at the individual, provider, and health care system levels, as well as mitigate challenges related to algorithmic bias, health equity, and validation of predictive models across diverse populations, will be needed.

Cancer Prevention and Screening Programs

The Centers for Disease Control and Prevention (CDC) continues to play a central role in promoting cancer prevention, increasing screening uptake, and reducing disparities in cancer outcomes through programs administered by the Division of Cancer Prevention and Control. CDC supports evidence-based screening through NBCCEDP, the National Comprehensive Cancer Control Program, and the Colorectal Cancer Control Program, while also providing public education campaigns and implementation resources to help health systems improve delivery of recommended cancer screening services, particularly among medically underserved populations (see **Sidebar 49**, p. 195). CDC has continued to expand its Cancer Screening Change Packages, which provide evidence-based strategies that health systems can use to increase screening rates, improve follow-up after abnormal findings, and reduce barriers to care (1115). In addition, CDC continues to advance initiatives focused on reducing disparities in cancer prevention and screening, including efforts to strengthen partnerships with community-based organizations and increase the proportion of women served through NBCCEDP who are up to date with cervical cancer screening.

Within CDC, the National Institute for Occupational Safety and Health (NIOSH) continues to play an important role in

SIDEBAR 49

DCPC Public Health Campaigns and Screening Tools

Screen for Life: National Colorectal Cancer Action Campaign

A national effort to increase **colorectal cancer** screening rates through public education and outreach—targeting adults age 45 and older, especially in underserved communities. The campaign promotes early detection to reduce mortality.

Inside Knowledge About Gynecologic Cancer Campaign

Focuses on educating women and health care providers about the signs, symptoms, and risk factors of **gynecologic cancers** (ovarian, uterine, cervical, vulvar, and vaginal). It empowers women to seek timely medical advice and promotes informed health care decisions.

Bring Your Brave Campaign

Designed to raise **breast cancer** awareness among younger women (ages 18 to 44), who may not be aware of their risk. The campaign encourages women to learn about breast health, recognize potential warning signs, and engage in early detection practices.

DCPC, CDC's Division of Cancer Prevention and Control.

identifying occupational carcinogenic hazards, monitoring workplace cancer risks, and developing strategies to reduce hazardous exposures among health care workers and other occupational groups. NIOSH continues to maintain and periodically update the NIOSH List of Hazardous Drugs in Healthcare Settings, which identifies hazardous drugs—including many antineoplastic agents and other carcinogenic compounds—and provides guidance to employers and health care facilities on safe handling practices to reduce occupational exposures associated with increased cancer risk. Following publication of the 2024 list, NIOSH issued additional updates in 2025 to incorporate newly approved hazardous drugs, ensuring that guidance keeps pace with advances in cancer therapeutics (1116).

Mitigating Modifiable Risk Factors

Certain health behaviors, lifestyle choices, and environmental exposures are considered modifiable risk factors for cancer (see **Reducing the Risk of Cancer Development**, p. 55). Federal evidence-based policies play an important role in reducing modifiable cancer risk by supporting vaccination, promoting healthy lifestyles, limiting exposure to environmental and occupational carcinogens, educating the public about cancer risk factors, and increasing uptake of proven preventive interventions.

One of the most effective cancer prevention interventions is vaccination against HPV, which is responsible for nearly all cervical cancers as well as many anal, vulvar, vaginal, penile, and oropharyngeal cancers (see **Prevent and Eliminate Infection From Cancer-causing Pathogens**, p. 71). In response to a presidential memorandum directing the secretary of HHS and the acting director of CDC to examine how peer nations structure their childhood vaccination schedules, on January 5, 2026, CDC announced a major revision to the US childhood and adolescent immunization schedule, reducing the recommended number of HPV vaccine doses from two (or three) to one (1117,1118). Notably, this schedule revision was issued without a recommendation from the Advisory Committee on Immunization Practices (ACIP), whose 17 sitting members had been dismissed by the secretary of HHS in June 2025 and replaced with new appointees (1119). While some evidence supports the efficacy of a single dose for preventing cervical cancer, experts have cautioned that published data do not yet confirm that one dose is as effective as two or three doses for preventing non-cervical HPV-associated cancers, and no outcomes beyond 12 years from vaccination have been reported, underscoring the need for continued surveillance (1120).

In addition, the changes to the vaccine schedule have prompted concerns about insurance coverage beyond 2026 as well as growing state-level variation in vaccine policy, as many states have announced they will no longer use federal guidance for vaccine recommendations (1121,1122). As a result, HPV vaccine coverage and access could increasingly depend on where one lives, further contributing to cancer disparities with significant implications for adolescent cancer prevention. The new ACIP also announced a comprehensive working group review of HPV vaccine efficacy, safety, and

dosing, further signaling that additional changes to the HPV recommendations may be forthcoming (1123). However, a federal court ruled in March 2026 that the HHS secretary had improperly fired and replaced the ACIP members, issuing a stay blocking some of the immunization schedule changes while legal challenges proceed (1124). Maintaining strong public confidence in ACIP and continuing to improve HPV vaccination coverage among adolescents and young adults will be critical to reducing the future burden of HPV-associated cancers.

Alcohol consumption represents another major modifiable cancer risk factor that has received renewed national attention. In January 2025, HHS released *Alcohol and Cancer Risk 2025*, a comprehensive review concluding that alcohol consumption increases the risk of at least seven types of cancer and recommending greater public awareness of alcohol's carcinogenic effects (1125). The report also called for legislative and federal action to require cancer warning labels on all alcoholic beverages; however, no updates to alcoholic beverage warning labels have been enacted. At the state level, in 2025, Alaska became the second state after California to require cancer warning signs at bars and liquor stores, and Connecticut, Pennsylvania, Massachusetts, and New Jersey introduced similar warning label legislation (1126).

UV exposure from both natural sunlight and indoor tanning devices is another well-established, modifiable cause of skin cancer. Indoor tanning bed use before age 20 can increase the risk of developing melanoma by nearly 50 percent and melanoma rates among tanning bed users are more than double those of non-users (341). Despite this evidence, in March 2026, FDA withdrew a proposed rule that would have banned anyone under the age of 18 from using tanning beds and required adults to sign a risk acknowledgment waiver prior to use (1127). Without a federal rule, tanning bed regulations continue to vary by state, with some already barring minors from using tanning beds, while others allow teen access with parental consent. CDC continues to maintain public education campaigns promoting sun-safe behaviors and discouraging indoor tanning as well as community strategies to prevent skin cancer (1128,1129).

Nutrition, obesity, and physical inactivity also remain major contributors to modifiable cancer risk. Federal agencies continue to support initiatives that encourage healthy dietary patterns, physical activity, and obesity prevention as part of broader efforts to reduce the burden of chronic diseases, including cancer. Continued implementation of evidence-based prevention policies across these risk factors will be essential to reducing future cancer incidence. Among modifiable cancer risk factors, tobacco use remains the leading cause of cancer death in the United States and continues to warrant focused policy attention.

Leveraging Policy to Reduce Tobacco-related Illness

Tobacco use remains the leading cause of preventable death in the United States, leading to the deaths of more than 490,000 people annually and costing the US economy over $600 billion in health care expenditures and lost productivity each year (246). A significant portion of these damages can be attributed to the 17 tobacco-related cancers, including the number one cause of cancer-related death in the United States, lung cancer. While cigarette smoking is the primary contributor to these negative health outcomes, all tobacco products cause harm.

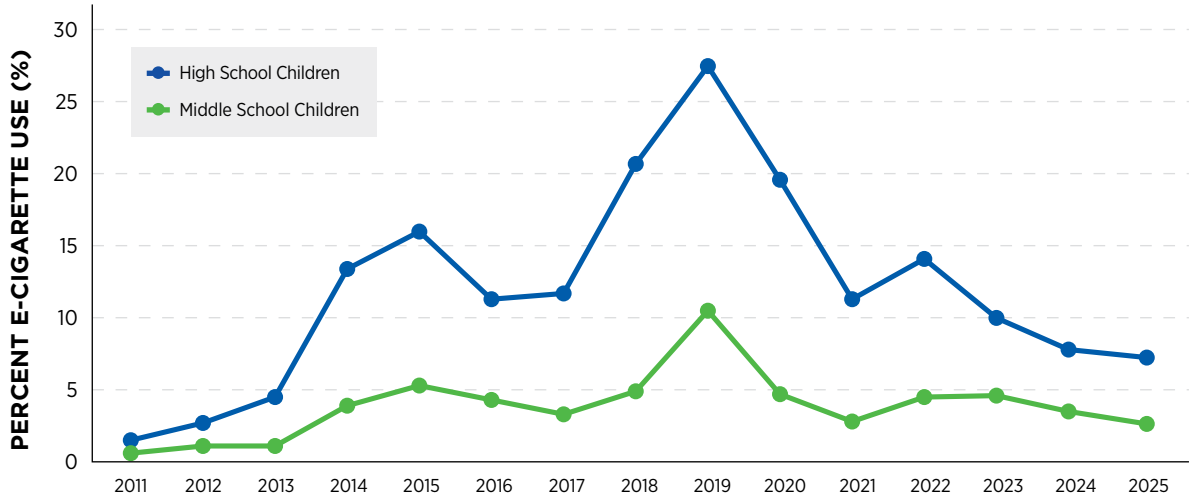
Fortunately, significant progress has been and continues to be made against tobacco use at the population level. According to the most recent readout of the National Health Interview Survey (NHIS) conducted by CDC, cigarette use among adults continues to fall, declining from 10.8 percent in 2023 to 9.9 percent in 2024. Despite significant marketing efforts by tobacco companies, the use of other tobacco products, including electronic cigarettes (e-cigarettes), remained unchanged (51). In addition, data from the 2025 National Youth Tobacco Survey (NYTS) conducted by FDA reported that 7.2 percent of youth were current tobacco product users and 5.2 percent used e-cigarettes (248). Both of these numbers constitute remarkable new lows and continue the downward trends in use seen in previous years (see **Figure 22**, p. 197).

However, this progress is not uniform across all tobacco products or all populations. While the NHIS was unable to evaluate changes in the use of nicotine pouches among adults due to a change in their classification between years, other studies have observed increases in the dual use of e-cigarettes and nicotine pouches as well as multi-product usage in youth and young adults (1130). The NYTS specifically highlights increases in nicotine pouch use among high schoolers between 2022 and 2025 (248). Additionally, much of the American South and Midwest, compared to other states, continue to experience a significantly higher burden of cancer deaths attributable to smoking (1131). Similar disparities persist based on race, ethnicity, education, sexual orientation, and urbanization levels (51), again due in no small part to targeted advertising.

To continue driving down tobacco use, increase progress in areas where disparities continue, and improve the health of all, robust federal research funding, regulation, and control programs are necessary. The CDC Office on Smoking and Health (OSH) and FDA Center for Tobacco Products (CTP) are two of the major federal offices coordinating these areas, significantly contributing to the positive trends seen to this point. However, the current Administration has significantly disrupted funding and staffing for these programs, despite sustained congressional support (1132). Highlighting the success of these offices and the clear return on investment they have provided, while also monitoring

FIGURE 22

Federal Programs Have Contributed to Decreasing E-cigarette Use Among Youth



SEP 2018
FDA expands The Real Cost youth anti-smoking campaign to also include e-cigarettes

DEC 2018
Surgeon General advisory declares youth e-cigarette use an epidemic

DEC 2019
Tobacco 21 law raises the federal minimum age for purchasing tobacco products

JAN 2020
FDA finalizes policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children

DEC 2021
Surgeon General links vaping to increased mental health issues

APR 2023
FDA limits vape sales and marketing targeting children

JUN 2024
FDA and DOJ form a task force to curb distribution and sale of illegal e-cigarettes

NOV 2024
Surgeon General releases report on tobacco-related health disparities

SEP 2025
Largest ever seizure of 4.7 million illegal e-cigarette units by FDA and CBP

E-cigarettes exploded in popularity prior to the COVID-19 pandemic, reaching peak use among youth in 2019. To protect young people from the dangers of tobacco use, new federal tobacco control efforts were initiated to meet the moment. Various programs, including anti-vaping advocacy campaigns, enforcement actions, and new policies and laws have helped curtail the youth e-cigarette epidemic. Unfortunately, new policies released by FDA and cuts at CDC in 2025 and 2026 threaten to allow e-cigarette use among youth to rise again.

CBP, US Customs and Border Protection; E-cigarette, electronic cigarette; DOJ, Department of Justice.

their ability to continue performing under these difficult circumstances, will be key to furthering the ongoing decreases in tobacco use and bettering public health.

Flavored Tobacco Products

Although cigarettes with characterizing flavors other than menthol were nationally prohibited in 2009, the addition of flavors to tobacco products remains prevalent. In general, the addition of flavor additives to combustible and non-combustible products increases their appeal, is associated with greater rates of tobacco use initiation, facilitates sustained use, and decreases rates of successful cessation (1133). Flavored electronic nicotine delivery systems (ENDS), which include e-cigarettes, are of particular scientific and public health interest because of their dual role as a primary driver of ENDS initiation and sustained use among youth and young adults, including those who are not cigarette users, while also being cited by adults who smoke as an important aid in quitting combustible cigarettes.

As a result of these risks to youth, FDA had been sparing in their marketing authorization of new e-cigarette products until 2026. However, this year, FDA authorized the sale of multiple new flavored e-cigarette products, including menthol-flavored

JUUL products and fruit-flavored products (1134,1135). This is particularly concerning, as flavored ENDS products pose, according to the FDA, a substantial risk to youth, and they pose a greater risk to youth than tobacco-flavored ENDS (1136). This authorization also came during a comment period on guidance positing situations in which flavored e-cigarettes might be authorized, prior to its closing and consideration of comments from the research community. Notably, these flavors were not among those highlighted in the guidance, since fruit-flavors are widely considered to be the most enticing and potentially harmful in terms of spurring youth uptake and sustained use. Given the known negative health effects of these products, as well as the potential carcinogenic effects that have been shown in laboratory studies to be exacerbated by flavoring (267,1137-1141), AACR maintains that flavored ENDS products should not be marketed until a clear benefit in aiding adults who smoke combusted cigarettes to quit is sufficiently validated, including the proviso that use of flavored ENDS products does not result in an increase in youth initiation of ENDS.

While increased authorizations of new flavored tobacco products are concerning, a joint FDA and Department of Justice (DOJ) task force was formed in the summer of 2024 to remove illegal e-cigarette products from the market and has made significant progress (1142). In the time since, the task force has performed multiple significant seizures of illegal products, and bipartisan legislation known as the S.T.O.P. Illicit Vapes Act is seeking to strengthen and codify its role (1143). However, FDA jeopardized public health by releasing a public statement in May 2026 outlining its decision to not prioritize enforcement against the vast majority of illegal flavored products (1144). Under this model, FDA would instead only actively enforce against those that look like everyday products such as candy or video games, which are especially dangerous as they explicitly target tobacco product use by children, or those products that do not have a pending marketing application submitted to FDA. Previously, FDA had received millions of applications (1145) and allowed these products to remain in stores despite their clear illegality but had not confirmed their intention to deprioritize enforcement.

Overall, the combination of decreased enforcement and increased authorizations of flavored products may lead to future increases in the use of newly introduced flavored tobacco products. Continued research is needed to monitor their use, identify their toxicities, verify any potential utility for smoking cessation, and create cessation strategies specific to these products. Efforts to curb overall youth tobacco use have resulted in historic lows (248), but these new policies could reverse years of progress.

Funding Federal Regulatory, Enforcement, and Control Activities

FDA CTP's regulatory and enforcement activities are entirely funded by user fees charged to manufacturers and importers of certain tobacco products. However, unlike all other tobacco product manufacturers, ENDS manufacturers do not pay user fees. To address this and provide FDA with the resources to more comprehensively enforce against illicit e-cigarette products, the bipartisan Resources to Prevent Youth Vaping Act was once again introduced in the 119th Congress (1146). Advancement of this bill would close an important loophole and is crucial to supporting future efforts to control tobacco use, as CTP has continued to face an outsized workload in relation to these products in comparison to staffing levels. Staffing levels were of particular concern this year, as the Administration's reduction in force policy led to the loss of hundreds of staff who had roles in enforcement, regulatory policy, public education campaigns, user fees, and contracting. Fortunately, a lawsuit from a coalition of state attorneys general resulted in the reinstatement of 229 employees (1147).

Despite this recent instability and its shift toward a pro-flavor and novel tobacco product stance, CTP has taken steps forward in some of the four key areas it oversees: regulation and guidance, compliance and enforcement, science and research, and public health education. FDA CTP's regulatory efforts are multifaceted, including product authorizations and rulemaking, among other roles. For example, FDA added 18 chemicals to its list of Harmful and Potentially Harmful Constituents (HPHCs) in tobacco products, providing clarity for the public on the dangers of tobacco products and updating the industry on which constituents are considerations in product review (1148). In terms of compliance and enforcement efforts in addition to the aforementioned FDA-DOJ task force, FDA has also issued warning letters and plans to send educational materials to tobacco companies and retailers selling unauthorized, illegal products. The agency has particularly targeted products that appear similar to everyday products such as handheld video games and candy, as well as flavored e-cigarette products (1149,1150).

While the FDA is overburdened with applications for flavored tobacco products, current administrative sentiments toward imported Chinese tobacco products present an opportunity for stricter regulations on all flavored products. FDA also continues to support tobacco regulatory science research and grant programs through collaboration with NIH (1151,1152). In addition, FDA's major cigarette and e-cigarette prevention efforts, known as The Real Cost campaigns, have continued to quantifiably decrease tobacco use among youth (1153). Although disrupted in 2025, recent studies have documented the program's successes throughout the years, including having prevented an estimated 444,252 US youth from initiating e-cigarette use between 2023 and 2024 alone (246,1154,1155). Given these successes and the return of staff to CTP, this program is slated to continue in future years (1156).

CDC OSH has also traditionally been a major player in federal efforts to control and reduce tobacco use and tobacco-related

harms. Unfortunately, nearly all of its activities have been negatively impacted by staffing cuts and budget instability (1132). CDC OSH's Tips From Former Smokers public education campaign has long encouraged people who smoke to quit through portrayals of real people living with smoking-related illnesses and has been documented to have helped over one million people quit and saved an estimated $7.3 billion in smoking-related health care costs between 2012 and 2018 alone (1157). Unfortunately, this program was terminated in 2025, and its status for future years is not known (1157). CDC OSH also is the only federal agency that provides funding and technical support to state and local health departments for tobacco control initiatives. This program has historically been highly successful, with every $1 spent on tobacco control programs having been shown to lead to a $55 return on investment, mostly through averted health care costs (1158).

While CDC OSH did receive level funding in FY 2026, the staffing cuts and uncertainty at the federal level have led to significant losses in state tobacco control efforts. Most states did receive funding from CDC OSH in 2026, but some states were not able to apply for funding as they traditionally did, and even more were forced to drastically reduce their services (1132). For example, Georgia's tobacco use prevention program, and West Virginia's Raze, a youth-led community organization funded by the state's tobacco prevention program, both closed due to these issues (1159). While Congress appears set to fund CDC OSH at a similar level in the upcoming FY 2027 budget bills, these funds will not have their intended effects if adequate staffing is not returned. Although, as noted previously, FDA CTP staff layoffs have been rescinded due to lawsuits, it remains unclear whether CDC OSH will receive similar treatment.

Addressing Cancer Disparities and Improving Patient Outcomes

As described in the *AACR Cancer Disparities Progress Report 2026*, cancer disparities are driven by a complex set of social, economic, environmental, geographic, structural, and biological factors that shape cancer risk, prevention, screening, diagnosis, treatment, clinical trial participation, survivorship, and outcomes. Despite decades of progress in cancer science and medicine, not all patients and communities have benefited equally from these advances. Disparities persist across the cancer continuum, affecting who is exposed to modifiable cancer risks, who is screened on time, who has access to high-quality care and clinical trials, who receives timely follow-up after an abnormal screening result, and who receives the support needed to live well after cancer treatment.

Science-based public policy is essential to ensuring that progress against cancer reaches all patients. Policymakers can help reduce disparities by sustaining federal investment in cancer disparities research, strengthening public health infrastructure, expanding access to evidence-based prevention and screening, improving clinical trial representation, supporting patient navigation and community health workers, protecting affordable insurance coverage, and investing in inclusive data systems that allow researchers and health care providers to identify gaps and measure progress. Research can identify the causes of unequal outcomes and point toward effective interventions, but policy determines whether those interventions reach the communities that need them.

Environmental Exposures and Cancer Risk

Cancer disparities can begin long before diagnosis in the environments where people live, work, learn, and grow up. Exposure to air pollution, industrial emissions, hazardous waste, radon, pesticides, per- and polyfluoroalkyl substances (PFAS), lead, and other harmful substances can increase the risk of cancer and other serious health conditions. These exposures are not distributed evenly. They often reflect

THE HONORABLE
Sanford D. Bishop Jr.
US Representative for Georgia's 2nd District

"My diagnosis did not change my commitment to cancer research. It underscored it. As someone guided by the teachings of Matthew 25, I have worked to ensure that everyone has access to health care that is modern, accessible, affordable, science-based, and backed by the research needed to eliminate health challenges facing my district and the country. That is what federal appropriations do. It funds the research, the hospitals, and the providers who give people relief from cancer and the other diseases they face.

"My message to anyone facing a diagnosis like mine is simple: address it as soon as possible. Early diagnosis means a much better chance of beating cancer and living a healthy life. I want all Americans to have access to the best care, built on the most modern scientific research, so we can conquer cancer once and for all."

differences in housing, land use, workplace protections, environmental monitoring, enforcement, and access to resources that help communities identify and reduce environmental harm.

Reducing exposure to known and suspected carcinogens is an important part of cancer prevention. Communities already facing barriers to screening, high-quality care, and economic opportunity should not also face weaker protections against environmental factors that may increase cancer risk. Policies that improve monitoring and enforcement, reduce exposure to harmful substances, support cleanup of contaminated sites, protect air and water quality, and incorporate meaningful community input can help lower modifiable cancer risks and improve health outcomes.

Federal agencies play a critical role in identifying environmental carcinogens, assessing risk, setting standards, enforcing protections, and providing communities with information about potential health hazards. The US Environmental Protection Agency (EPA) has long helped provide the scientific framework for evaluating cancer risks from chemicals and other environmental agents, including through its carcinogen risk assessment guidelines and related risk assessment tools (1160). These assessments inform regulatory decisions, guide public health protections, and help ensure that policies affecting air, water, soil, workplaces, and consumer products are grounded in the best available science.

Recent federal budget proposals and regulatory actions have raised concerns about the strength and durability of environmental health protections. The Administration's FY 2026 budget proposal included a 55 percent reduction in EPA funding and proposed eliminating or reducing several programs that help address air quality, emissions reduction, environmental monitoring, and community protection (1161). These proposed cuts include complete removal of several programs, including environmental justice, the Atmospheric Protection Program, and the Diesel Emissions Reduction Act Grants, among others. Alongside these cuts, on February 12, 2026, EPA's 2009 Greenhouse Gas Endangerment Finding was rescinded, repealing all greenhouse gas emission standards for vehicles and engines (1162). While climate policy extends beyond cancer alone, decisions that affect air quality, pollution exposure, occupational risks, environmental monitoring, and enforcement can have important implications for cancer prevention and public health.

Other federal decisions may also affect the ability of agencies and communities to identify and reduce cancer-related environmental risks. For example, changes in pesticide review, chemical risk assessment, or enforcement capacity could affect how quickly potential carcinogenic hazards are identified, evaluated, and addressed (1163). Because many environmental exposures are cumulative and long-term, delays or gaps in assessment and enforcement can leave communities with fewer tools to understand and reduce risks.

When discussing these threats to environmental research, it is essential to underscore how marginalized and socioeconomically disadvantaged populations can be disproportionately affected. More in-depth discussions around these complex societal concerns, such as redlining, are discussed in the *AACR Cancer Disparities Progress Report 2026* (16).

Protecting people from environmental cancer risks requires science-based decision-making, strong public health infrastructure, and sustained federal capacity. Policymakers should ensure that EPA and other federal agencies have the resources, expertise, and independence needed to assess carcinogenic hazards, enforce environmental protections, support communities facing elevated exposures, and reduce modifiable cancer risks. Cancer prevention does not begin only in the clinic. It also begins in the places where people live, work, and grow up.

Patient-centered Care and Outcomes and Survivorship

Each person diagnosed with cancer has a unique experience, ranging from successful treatment and living cancer-free to experiencing side effects or subsequent cancer diagnosis. As of May 2025, there are an estimated 18.6 million cancer survivors, with that number expected to grow to 22.4 million by 2035 (13). This is a triumph of research and medicine, but has posed a new question for policymakers: How do we address the unique lifelong needs of cancer survivors? Without federal support, current survivorship care is subprime and can lead to survivors facing unaddressed needs and continuing symptoms.

Reintroduced in 2026 by Representatives Debbie Wasserman Schultz (D-FL), Brian Fitzpatrick (R-PA), Mark DeSaulnier (D-CA), and Joe Wilson (R-SC), the Lainie Jones Comprehensive Cancer Survivorship Act seeks to address the entire continuum of care and work with cancer survivors on their unique needs following their active treatment (1164). This wide-scale legislation would enact programs including a cancer survivor employment assistance program and provide Medicaid coverage of cancer fertility services for survivors, among many other policies.

The relationship between the patient, the health care provider, and the support network is essential for discussions around survivorship. Close and long-term working relationships among all parties are a necessary tool in addressing the complex needs of survivors, and even in preventing subsequent cancers. Working to develop a survivorship care plan with a

health care provider, which would constitute a detailed a record of a patient's cancer and treatment history, can help patients have their needs better understood and find tailored support and services (1165,1166).

Improving the Use of Digital Information in Cancer Treatment and Management

Digital health technologies and AI are transforming patient outcomes by improving clinical decision-making, supporting earlier diagnosis, personalizing treatment, and enhancing survivorship care. Realizing the full potential of these technologies depends on the ability to securely collect, integrate, and exchange high-quality health data across health care systems. Despite widespread adoption of electronic health records, oncology data remain fragmented across providers, laboratories, pharmacies, imaging centers, and insurers, limiting the ability of clinicians and researchers to obtain a comprehensive understanding of a patient's medical history. In addition, important information, including patient reported outcomes, genomic data, social drivers of health, race, ethnicity, sexual orientation, gender identity, and treatment toxicity, is often collected inconsistently or stored in nonstandard formats, limiting its usefulness for clinical care, quality improvement, and research (1167,1168).

Federal agencies continue to advance policies intended to improve interoperability and promote responsible use of AI in health care. Within HHS, the Assistant Secretary for Technology Policy/Office of the National Coordinator for Health Information Technology (ASTP/ONC) has continued implementation of the Health Data, Technology, and Interoperability (HTI-1) Final Rule, which establishes transparency requirements for predictive decision support interventions incorporated into certified health information technology (1169). These policies are intended to improve clinicians' understanding of how AI-enabled tools generate recommendations while promoting safer, more transparent, and more equitable use of AI in clinical practice. In June 2026, HHS also announced new steps to strengthen implementation of the Trusted Exchange Framework and Common Agreement, expanding nationwide exchange of electronic health information and facilitating more seamless sharing of patient records across participating health systems (1170). Improved interoperability is particularly important in oncology, where patients frequently receive multidisciplinary care across multiple institutions and where comprehensive clinical data are essential for precision medicine and survivorship care.

Federal investment in programs such as the NCI's Childhood Cancer Data Initiative (CCDI) continue to demonstrate the value of robust, interoperable data systems for improving patient outcomes. CCDI is creating a national data ecosystem that aims to collect and securely share clinical and research information from children, adolescents, and young adults diagnosed with cancer (1171). By enabling researchers and clinicians to access standardized, longitudinal data across institutions, CCDI has the potential to accelerate discoveries for rare cancers (including pediatric cancers), improve clinical decision-making, facilitate survivorship research, and support the development of more personalized therapies. In 2025, HHS announced it would double the funding for the CCDI to better incorporate AI and further accelerate progress (1172). Continued investment in interoperable health information infrastructure and trustworthy AI will be critical to ensuring that advances in digital medicine translate into improved outcomes for all patients with cancer.

AACR Call to Action

The progress described in this report is measured in lives saved. Since 1991, the overall cancer death rate in the United States (US) has declined by 35 percent, translating to more than 4.8 million fewer cancer deaths. Today, there are more than 18.6 million cancer survivors.

Behind these numbers are advances across the cancer continuum. New approaches to prevention and early detection, increasingly precise ways of diagnosing and treating cancer, and innovative therapies are helping patients live longer, healthier lives. These achievements would not have been possible without strong bipartisan leadership in the US House of Representatives and Senate, which have long made medical research a national priority.

For this progress to continue, Congress must act decisively to provide a robust increase in funding for the National Institutes of Health (NIH) in fiscal year (FY) 2027 and protect a federal grantmaking process grounded in scientific merit.

Therefore, at this pivotal moment, the American Association for Cancer Research (AACR) calls on Congress to stop the Office of Management and Budget (OMB) from finalizing or implementing its proposed rule, "Regulation for Federal Financial Assistance." The proposal would inject political considerations into funding decisions and broaden federal agencies' authority to terminate grants for reasons unrelated to scientific merit or recipient performance. While we commend the Senate for its bipartisan action to block the rule through December 11, 2026, a temporary delay is not a lasting solution. Congress must carry this protection forward in final FY 2027 appropriations legislation and ensure that federal grantmaking remains guided by evidence, scientific merit, transparency, and accountability.

In summary, continued progress against cancer and the hundreds of diseases affecting millions of Americans will require the unwavering support of our elected leaders to:

Sustain the Foundations of Discovery

- **Provide robust and sustained federal investments for medical and cancer research.** Congress should provide at least $51.303 billion for NIH and at least $7.999 billion for the National Cancer Institute (NCI) in FY 2027. This funding is essential to maintaining a broad and competitive research portfolio and advancing the discoveries that will define the next era of progress against cancer and all of the other diseases affecting so many Americans. NIH-supported research also fuels economic activity, supports jobs, and drives innovation at universities, medical centers, and small businesses across the country.
- **Ensure that federal research funds are implemented as Congress intended.** The current Administration has prevented appropriated funds from being awarded in a timely and predictable manner and administered without unnecessary delay or interference. The Administration should also ensure that NIH has the sufficient staffing and expertise to manage every stage of the grantmaking process, from application receipt and merit review to award administration and closeout. When funding is delayed, narrowed, redirected, or structured in ways that reduce the number of meritorious grants supported, such as through the Administration's mandate to utilize the multi-year funding mechanism without a corresponding increase in resources, the consequences are felt in laboratories, clinical studies, training programs, and ultimately in the lives of patients waiting for better options.
- **Prioritize the cancer research workforce.** Early-career and early-stage investigators are the future of cancer research. Federal policies must create stable pathways for promising scientists to establish independent careers, pursue bold ideas, and build the research programs that will produce tomorrow's breakthroughs against cancer.

Protect Scientific Integrity and Independence

- **Preserve scientific merit as the foundation of federal research funding.** Funding decisions should be guided by rigorous evaluation by scientific experts, not political or ideological considerations. Congress and the Administration should reject policies that subject research grants to political review or allow meritorious proposals to be denied on undefined or nonscientific grounds.
- **Safeguard the stability of active research awards and clinical trials.** Active research grants, including awards supporting ongoing clinical trials, should

not be terminated for reasons unrelated to recipient performance, scientific integrity, or responsible stewardship of federal funds. Because of the complexities of cancer, cancer research often requires years of sustained investment. Abruptly withdrawing support wastes taxpayer resources, destabilizes research programs, and jeopardizes studies on which patients depend.

- **Protect researchers' ability to publish and share scientific findings to maximize innovation.** Researchers must be able to access scientific literature, participate in scientific conferences, and exchange knowledge with colleagues. These activities are essential to validating discoveries, fostering innovation, avoiding unnecessary duplication, informing patient care, and ensuring that the public benefits from taxpayer-funded research.
- **Apply rigorous, risk-based oversight to international scientific collaboration.** Protecting research integrity and national security is essential, but oversight should be targeted and proportionate to risk. Broad or unnecessary barriers to legitimate international partnerships would limit access to specialized expertise, data, technologies, and patient populations and would weaken American scientific leadership.

Scientific integrity is what makes research credible and medical advances worthy of public trust.

Ensure That Every Patient Benefits From Progress Against Cancer

- **Strengthen the US Food and Drug Administration's ability to translate discoveries into benefits for patients.** Policymakers should ensure that the agency has the oncology expertise and regulatory science capacity needed to support modern, patient-centered clinical trials while maintaining rigorous standards for safety and effectiveness.
- **Sustain evidence-based public health programs that prevent cancer and promote earlier detection.** The Centers for Disease Control and Prevention and other US public health agencies must have the resources, expertise, and independence needed to support screening, tobacco control, vaccination, and other proven cancer prevention strategies. Their guidance and policies should reflect the best available scientific evidence.
- **Modernize the infrastructure that connects research and care.** Policymakers should invest in interoperable data systems, responsible digital health technologies, the cancer workforce, and community-based care infrastructure. These investments are essential to delivering complex cancer care, accelerating research, and extending the benefits of discovery across the country.
- **Remove barriers to cancer prevention and care.** Policymakers should expand access to evidence-based prevention and screening services, broaden participation in clinical trials so that study populations better reflect the people affected by cancer, and support comprehensive treatment and survivorship care. Rural and medically underserved communities, people with limited insurance coverage, and populations that have historically experienced worse cancer outcomes must be central to these efforts, not an afterthought.

Cancer is not partisan. It remains one of the most urgent and universal challenges of our time, touching not only patients and survivors but also the families, friends, and caregivers who stand beside them. For more than 50 years, the United States has led the world in confronting this disease through sustained federal investment, bipartisan resolve, and an enduring commitment to scientific progress that improves and saves lives.

Continued advances depend on robust federal funding for medical research and a grantmaking system that allows the strongest science to move forward without political interference. The decisions Congress makes now will determine whether the United States continues to lead the world toward a future without cancer.

AACR Initiatives

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Mission

The mission of the American Association for Cancer Research (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.org/Member

- AACR membership includes more than 65,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 143 countries and territories around the world.
- Presently, 34 percent of members live outside the United States and 20 percent of AACR's international members are located in countries building cancer research capacity.
- AACR-Minorities in Cancer Research (MICR) and AACR-Women in Cancer Research (WICR), AACR support 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
AACRJournals.org

- 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.
- The AACR Cancer Progress Reports are a cornerstone of AACR's educational and advocacy efforts. The purpose of report(s) is to inform Congress and the American public about the unprecedented progress against cancers; underscore the importance of and advocate for federal funding for cancer research; highlight the current challenges; and emphasize the urgent need to address cancer health disparities, with the overarching goal to achieve health equity for all people, regardless of their race, ethnicity, age, gender, sexual orientation, socioeconomic status, or geographic location.
- Other AACR publications include the *AACR Annual Impact Report* and the blog *Cancer Research Catalyst*.

AACR Grants Program
AACR.org/Funding

- 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 $551 million in funding for cancer research projects in the United States and 32 countries abroad.

Meetings
AACR.org/Calendar

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 2–7, 2027, in Orlando, Florida.

Policy and Advocacy
AACR.org/Policy

- 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.org/Genie

AACR Project GENIE® is an open-source, international, pan-cancer registry of real-world data assembled through data sharing between a cohort of 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
AACR.org/Foundation

The AACR Foundation provides vital philanthropic support for AACR. Funds raised by the AACR Foundation from individuals, foundations, corporate partners, and others help make AACR's groundbreaking programs and initiatives possible, advancing the shared mission to prevent and cure all forms of cancer.

Professional Development
CancerCareers.org

AACR supports education and training of cancer scientists and clinicians and provides professional development opportunities and resources to enhance and advance their careers. AACR's 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.

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