AACR CANCER PROGRESS REPORT 2025

AACR CANCER PROGRESS REPORT 15 YEARS 2011 – 2025

Spotlight on
ADVANCES IN
BLOOD CANCER

UNIFYING
CANCER SCIENCE AND
MEDICINE:
A CONTINUUM OF
INNOVATION
FOR **IMPACT**

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UNIFYING CANCER SCIENCE AND MEDICINE: A CONTINUUM OF INNOVATION FOR IMPACT

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"We've got to beat this disease. And the only way to do that is by funding research."

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Steering Committee

Lillian L. Siu, MD, FAACR, FRCPC
Steering Committee Chair
AACR President 2025–2026
Professor, University of Toronto
Medical Oncologist, Princess Margaret Cancer Centre
Director, Phase I Clinical Trials Program
BMO Chair in Precision Cancer Genomics
Princess Margaret Cancer Centre, University Health Network
Toronto, Ontario, Canada

Peter J. Allen, MD
David C. Sabiston, Jr. Distinguished Professor of Surgery
Chair, Department of Surgery
Chief, Division of Surgical Oncology
Health System Vice President for Cancer Services
Member of the Duke Cancer Institute
Duke University School of Medicine
Durham, North Carolina

Kenneth C. Anderson, MD, PhD (hc)
Kraft Family Professor of Medicine at Harvard Medical School
Director, LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Doris Duke Distinguished Clinical Research Scientist
American Cancer Society Clinical Research Professor
Boston, Massachusetts

Michael A. Carducci, MD, FACP, FASCO
AEGON Professor in Prostate Cancer Research
Vice Chair for Solid Tumor Oncology
Member, Miller-Coulson Academy of Clinical Excellence
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

Andrew E. Chapman DO, FACP, FCPP
Director, Sidney Kimmel Comprehensive Cancer Center
EVP Cancer Research and Oncology Services, Jefferson
Professor of Medical Oncology
Clinical Professor, Jefferson College of Nursing
Co-Director, Jefferson Senior Adult Oncology Center
Philadelphia, Pennsylvania

Steven J. Chmura, MD, PhD
Professor of Radiation and Cellular Oncology
Professor of Medicine
Professor of Neurological Surgery
Medical Director, Comprehensive Cancer Center
Director, Clinical and Translational Research for Radiation Oncology
University of Chicago Medicine
Chicago, Illinois

Margaret Foti, PhD, MD (hc)
Chief Executive Officer
American Association for Cancer Research
Philadelphia, Pennsylvania

Sophia H. L. George, PhD
Professor, Department of Ob, Gyn and Reproductive Sciences
Division of Gynecologic Oncology
Associate Director, Sylvester Comprehensive Cancer Center
University of Miami Miller School of Medicine
Miami, Florida

Lucy A. Godley, MD, PhD
Jeffrey and Marianne Silver Family Professor of Oncology
Professor, Medicine (Hematology and Oncology)
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Ana P. Gomes, PhD
Principal Investigator
Associate Member, Department of Molecular Oncology
Moffitt Cancer Center
Tampa, Florida

Carmen E. Guerra, MD, MSCE, FACP
Ruth C. and Raymond G. Perelman Professor and Vice Chair, Medicine
Associate Director of Community Outreach and Engagement, Abramson Cancer Center
Perelman School of Medicine, University of Pennsylvania
Philadelphia, Pennsylvania

Trey Ideker, PhD
Professor, Department of Medicine
Adjunct Professor, Departments of Bioengineering and Computer Science
Member, Moores Cancer Center
Director, ARPA-H ADAPT, Dynamic Digital Tumors for Precision Oncology
Director, Bridge2AI Cell Maps for AI
Co-Director, Cancer Cell Map Initiative
University of California San Diego
La Jolla, California

Meredith S. Irwin, MD
Chief of Paediatrics, Oncologist and Senior Scientist
The Hospital for Sick Children (SickKids)
Professor and Chair, Department of Paediatrics, Temerty Faculty of Medicine
University of Toronto
Toronto, Ontario, Canada

Marcela V. Maus, MD, PhD
Paula J. O'Keeffe Endowed Chair of the Massachusetts General Hospital Cancer Center
Director, Cellular Immunotherapy Program
Professor, Hematology and Oncology, Massachusetts General Hospital and Harvard Medical School
Boston, Massachusetts

Sandra S. McAllister, PhD
Associate Professor of Medicine, Harvard Medical School
Co-Director, Aging and Cancer Research Labs, Division of Hematology, Brigham & Women's Hospital
Member, Breast Cancer Program, Dana-Farber/Harvard Cancer Center
Member, Mass General Brigham Cancer Institute
Associate Member, Broad Institute
Boston, Massachusetts

Jason A. Mendoza, MD, MPH
Professor and Associate Program Head, Cancer Prevention Program, Fred Hutchinson Cancer Center
Associate Director, Community Outreach and Engagement, Fred Hutch/UW/ Seattle Children's Cancer Consortium
Professor, University of Washington, Seattle Children's Research Institute
Seattle, Washington

John M. Salsman, PhD
Director of Clinical Research in Adolescent and Young Adult (AYA) Oncology and Co-Leader, Cancer Prevention and Control Program, Atrium Health Wake Forest Baptist Comprehensive Cancer Center
Professor, Social Sciences and Health Policy & Associate Director, Public Health Sciences, Wake Forest University School of Medicine
Winston-Salem, North Carolina

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AACR Staff

Rajarshi Sengupta, PhD
Senior Director, Scientific Research Analysis and Dissemination

Sayyed Kaleem Zaidi, PhD
Deputy Director, Scientific Research Analysis and Dissemination

Elizabeth Blackman, MPH, PhD
Scientific Research Analyst, Scientific Research Analysis and Dissemination

Kristin Primm, MPH, PhD
Scientific Research Analyst, Scientific Research Analysis and Dissemination

Brett M. Sansbury, PhD
Senior Scientific Research Analyst, Scientific Research Analysis and Dissemination

Heather M. Clark
Senior Web/Print Designer, Marketing, Creative Services, and Multimedia Production

Joshua F. Goldstein
Senior Director, Brand Strategy Communications, Communications and Public Relations

Jenna M. Bachen
Senior Creative Director, Marketing, Creative Services, and Multimedia Production

Richard G. Buck
Chief Communications Officer and Vice President, Communications and Public Relations

Brad Davidson, PhD
Regulatory Science and Policy Analyst, Office of Science Policy and Government Affairs

Paul J. Driscoll, Jr.
Chief Marketing Officer and Vice President, Marketing, Creative Services, and Multimedia Production

Araceli Estrada
Senior Manager, Patient Advocacy, Office of Science Policy and Government Affairs

Matt Gontarchick
Associate Director, Government Affairs, Office of Science Policy and Government Affairs

Andrew Matthius
Senior Writer and Editor, Communications and Public Relations

Carly McCallie
Director, Government Affairs, Office of Science Policy and Government Affairs

Jon G. Retzlaff, MBA, MPA
Chief Policy Officer and Vice President, Office of Science Policy and Government Affairs

Blake Rostine
Senior Manager, Government Affairs, Office of Science Policy and Government Affairs

Carrie Treadwell, MBA
Senior Director, Strategic Patient Advocacy and Engagement, Office of Science Policy and Government Affairs

Rukiya Umoja, PharmD, RPh
Associate Director, Regulatory Science and Policy, Office of Science Policy and Government Affairs

David Zahavi, PhD
Senior Science Policy Analyst, Office of Science Policy and Government Affairs

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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 58,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 141 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. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting. 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 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. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit **AACR.org.**

Message From AACR

Launched in 2011 to commemorate the 40th anniversary of the landmark National Cancer Act of 1971, which galvanized national efforts to conquer cancer, the *AACR Cancer Progress Report* series celebrates its 15th year in 2025. This milestone is a testament to the extraordinary progress against cancer that has been catalyzed by decades of transformative medical research and technological innovation. Discoveries across basic, translational, clinical, and population sciences are driving breakthroughs in cancer medicine, leading to a steady decline in overall US cancer death rate and allowing more people to live longer, fuller lives after a cancer diagnosis. Improvements in cancer prevention and early detection have averted an estimated 4.75 million deaths from five major cancer types over the past 45 years, underscoring the pivotal role of public health measures alongside medical innovation. As of January 1, 2025, the number of cancer survivors in the United States reached 18.6 million, a significant increase from the 12 million survivors reported in our inaugural report, and this number is projected to surpass 22 million by 2035.

Among the most critical drivers of the progress against cancer are precision medicine and cancer immunotherapy, which are revolutionizing how cancer is diagnosed and treated. When the first report was published in 2011, there were no cellular immunotherapies, and only one immune checkpoint inhibitor had been approved by the US Food and Drug Administration (FDA). As of June 30, 2025, nine adoptive cell therapies have been approved, including the most recent groundbreaking T-cell receptor T-cell therapy for synovial sarcoma, and 15 immune checkpoint inhibitors are available for treating more than 20 cancer types.

Innovations in molecularly targeted therapeutics continue to fuel precision medicine, such as the approval of the first menin inhibitor for acute myeloid leukemia; promising advances for patients with rare cancers, including the first IDH1/2 inhibitor for low-grade glioma; and the first-ever HER3-targeted therapy for NRG1 fusion–positive lung and pancreatic tumors. This year we also report FDA approvals of two new antibody–drug conjugates, a rapidly growing class of therapeutics, for the treatment of breast and lung cancers.

These remarkable advances are a direct result of sustained federal investments in medical research and regulatory science, particularly through National Institutes of Health (NIH), National Cancer Institute (NCI), Centers for Disease Control and Prevention (CDC), and FDA. However, this progress is now at risk. In fiscal year (FY) 2024, Congress reduced NIH funding for the first time in nearly a decade, and in 2025—a year marked by grant delays, canceled clinical trials, mass layoffs in the research workforce, and political interference—the cancer research and care community is facing its most serious funding crisis in a generation. Past funding reductions, such as those caused by the 2013 sequestration process, forced laboratories to shutter, some of which never resumed work, and delayed the development of high-potential therapies among other setbacks. Without robust, sustained, and predictable annual increases in funding, we risk reversing hard-won progress against cancer. In this regard, it is encouraging to see a bipartisan Senate effort not only to maintain current funding levels, but also to increase support for medical research, reaffirming the federal commitment to saving lives.

The need for robust support is underscored by the fact that cancer still exacts a heavy human and economic toll across the nation and around the world. More than two million people in the United States are expected to be diagnosed with cancer in 2025, and over 600,000 will die from the disease. Around the globe, the incidence of certain cancers—including colorectal, breast, gastric, and others—is rising among adults under 50. Stark disparities remain, with medically underserved communities bearing a disproportionate cancer burden. At the same time, the future of the scientific workforce is at risk. The declining NIH payline leaves many early-career and early-stage investigators unable to launch independent research careers, particularly in underfunded areas such as pediatric and rare cancers. Young investigators are the backbone of future scientific innovation, driving fresh ideas and bold discoveries, and the nation must do more to support them. To help address the current medical research funding crisis, AACR has launched its largest-ever grant program to provide $15 million in support of early-stage and mid-career cancer researchers, ensuring that talented scientists at critical points in their careers can continue advancing lifesaving discoveries.

Despite serious challenges, the resilience of cancer researchers and the momentum of scientific discovery have never been stronger. Emerging technologies are opening new frontiers in how we understand, detect, and treat cancer. Artificial intelligence is poised to transform every aspect of cancer research and patient care, from drug discovery and diagnostics to clinical decision-making and survivorship care. Innovative tools such as liquid biopsies and multi-cancer early detection tests promise to identify cancer at earlier, more treatable stages. Exciting

advances in cancer vaccines, including those leveraging mRNA platforms, hold the potential to both prevent and treat intractable diseases, such as pancreatic cancer and kidney cancer. Meanwhile, next-generation molecularly targeted therapies, such as protein degraders, molecular glues and mutant-specific inhibitors, are expanding our ability to tackle some of the most elusive cancer targets. These and other breakthroughs on the horizon reaffirm that with sustained investment and scientific ingenuity, we can dramatically accelerate the pace of progress for the benefit of cancer patients.

Realizing this promise will depend on scientific innovation and on our ability to foster collaborations across disciplines, sectors, and borders. Initiatives such as AACR Project GENIE® and other pioneering efforts led by AACR and other organizations exemplify the power of global cooperation to drive scientific breakthroughs and ensure that patients around the world benefit from the latest advances.

The *AACR Cancer Progress Report 2025* is both a celebration of what cancer science and medicine have delivered and a Call to Action to safeguard its future. The evidence is clear: federal investments in cancer research yield extraordinary returns in lives saved, suffering reduced, and hope restored. To continue advancing toward a future where cancer is preventable, treatable, and curable for all, Congress must act to ensure robust, sustained, and predictable funding increases for the NIH, NCI, FDA, and CDC, and invest in the next generation of cancer researchers and physician-scientists.

Together, with bold vision, bipartisan leadership, and unwavering commitment, we can build on 15 years of progress against cancer and continue transforming cancer care for our patients everywhere.

Lillian L. Siu, MD, FAACR, FRCPC
President, AACR

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

Executive Summary

We are making remarkable strides against the collection of diseases known as cancer. Breakthroughs across basic, translational, clinical, and population sciences—combined with rapid technological innovation—are transforming how we prevent, detect, diagnose, and treat cancer.

As the first and largest professional organization in the world dedicated to preventing and curing all cancers, the American Association for Cancer Research (AACR) remains committed to enhancing public understanding of cancer and advocating for robust, sustained, and predictable investment in medical research—investment that is essential to saving lives. This includes steadfast support for the US federal agencies that fuel progress against cancer, particularly the National Institutes of Health (NIH), National Cancer Institute (NCI), Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC).

However, the significant gains made in cancer science and medicine are under threat. Recent disruptions to the federal workforce, along with growing uncertainty about the future of medical research funding, pose a grave risk to the scientific enterprise. Any erosion of support for NIH would have a catastrophic impact on future discoveries and delay lifesaving advances for patients and families. It is therefore encouraging to see a bipartisan effort in the Senate not only to maintain current funding levels, but also to increase support for medical research and continue the federal investment in saving lives.

Now in its 15th edition, the *AACR Cancer Progress Report* series to Congress and the American public is a major cornerstone of our educational and advocacy efforts. Over the past decade and a half, these reports have showcased the extraordinary momentum in cancer research and how sustained federal investment has led to improvements in treatment options, survival, and quality of life for cancer patients. This year's report continues that tradition—highlighting how medical research can transform the lives of cancer patients, including those of the nine courageous individuals featured in this report. It also makes clear that continued progress hinges on unwavering support for NIH, NCI, FDA, and CDC and on a stable research infrastructure that can deliver advances for the benefit of all patients affected by this dreadful disease.

Cancer in 2025

Significant progress against cancer has led to a steady decline in cancer death rates and a consistent increase in the number of individuals living longer, fuller lives after a diagnosis. In the United States, the overall cancer death rate decreased by 34 percent between 1991 and 2023, a reduction that translates into averting more than 4.5 million deaths from cancer. This reduction in cancer mortality is largely attributable to national public health efforts, including prevention initiatives, screening programs, and advancements in treatment for certain cancers.

The steady progress in reducing cancer mortality is largely driven by reduced smoking rates and subsequent decline in lung cancer deaths, a trend that has accelerated in recent years due to advances in treatment and early detection. Steady declines in death rates for colorectal cancer and female breast cancer since the 1990s have also played a key role in reducing the overall cancer mortality. More recently, advances in precision medicine have led to reductions in death rates for leukemia, melanoma, and kidney cancer, further contributing to overall progress. Thanks to the research-driven advances across the cancer care continuum, approximately 18.6 million individuals with a history of cancer were living in the United

Average Annual Decline in US Cancer Death Rates (2011–2023)

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States as of January 1, 2025, and this number is projected to exceed 22 million by 2035.

While remarkable progress has been made, cancer remains a major public health challenge in the United States and globally. In the United States, more than two million new cases are projected for 2025 alone, underscoring the urgent need for continued investment in research, prevention, early detection, and equitable access to care.

One of the key challenges we face is the uneven progress across cancer types. For example, the overall 5-year relative survival rate remains just 13 percent for pancreatic cancer and 6 percent for glioblastoma multiforme, an aggressive form of brain cancer, compared to 92 percent for breast cancer and 98 percent for prostate cancer. Additionally, the burden of cancer continues to disproportionately affect racial and ethnic minority groups and other medically underserved populations in the United States. These disparities are driven by a long history of structural inequities and systemic injustices and are driven by complex and interrelated structural and social factors.

The burden of cancer and its economic toll, both on individuals and on US health care systems, are expected to rise in the coming decades, underscoring the urgent need for more research in medicine and public health to accelerate the pace of progress against cancer. The progress highlighted in this report was made as a direct result of the cumulative efforts of individuals working across the spectrum of medical research supported by federal funding. Importantly, public sector funding from NIH and NCI directly benefits patients through the development of lifesaving anticancer therapeutics and preventive interventions.

Recent funding cuts and proposed budget reductions will stall progress, disrupt the research enterprise, and jeopardize future discoveries. Without strong federal support for medical research, the United States risks falling behind in scientific innovation and losing momentum in efforts to prevent, treat, and ultimately cure cancer. Continued federal investments in NIH, NCI, FDA, and CDC are essential to preserve US leadership in medical research, support the next generation of cancer researchers, and ensure that future breakthroughs translate into longer, healthier lives for everyone.

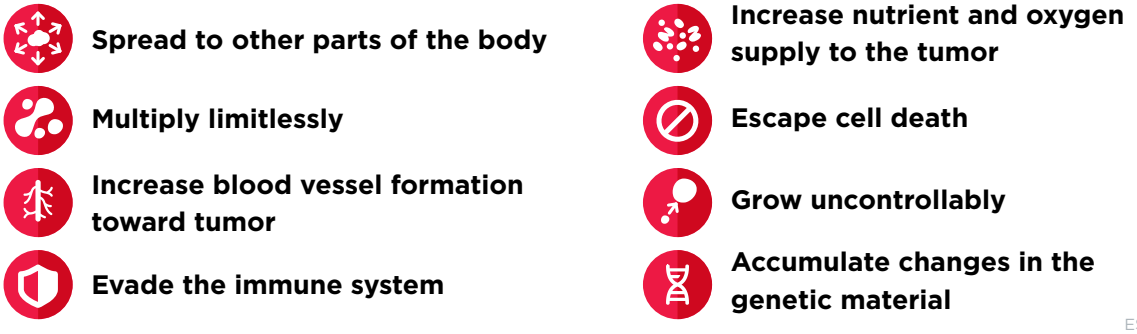
Understanding the Path to Cancer Development

Decades of basic research have established cancer as a collection of diseases characterized by the uncontrolled growth of cells. Cancer development is driven by disruptions of the molecular and cellular functions that regulate how cells grow, divide, and survive. Many of these changes are often just 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 acquire changes that make their genome unstable, divide limitlessly, grow uncontrollably, escape cell death, spread to other tissues in the body, evade destruction by the immune system, and increase nutrients and oxygen supply to tumors.

One of the hallmarks of cancer cells is alterations in the DNA sequence, also called genetic mutations. There are two types of genetic mutations associated with cancer: germline and somatic. Germline mutations are inherited and 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 are acquired throughout a person's lifetime and can arise in multiple ways, such as due to errors made during cell division, or in response to environmental exposures, lifestyle factors, or because of chronic health conditions. In addition to DNA mutations,

Hallmarks of Cancer Cells



other changes inside the cell—including RNA variations, protein modifications, and epigenetic alterations—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 circulatory and immune systems, 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 the tumor microenvironment (TME). Research has shown that the TME affects the growth of cancer cells, and cancer cells influence the TME to promote their survival.

Technological advances have made it possible to study cancer at the levels of single cells and molecules, revealing that each patient's cancer is unique. This foundational insight is the basis for precision medicine, or personalized medicine, which is broadly defined as treating patients based on molecular characteristics that distinguish them from other individuals with the same disease. Rapid developments in precision medicine are yielding new and effective ways to make a diagnosis, plan treatment, and predict and monitor treatment response.

Reducing the Risk of Cancer Development

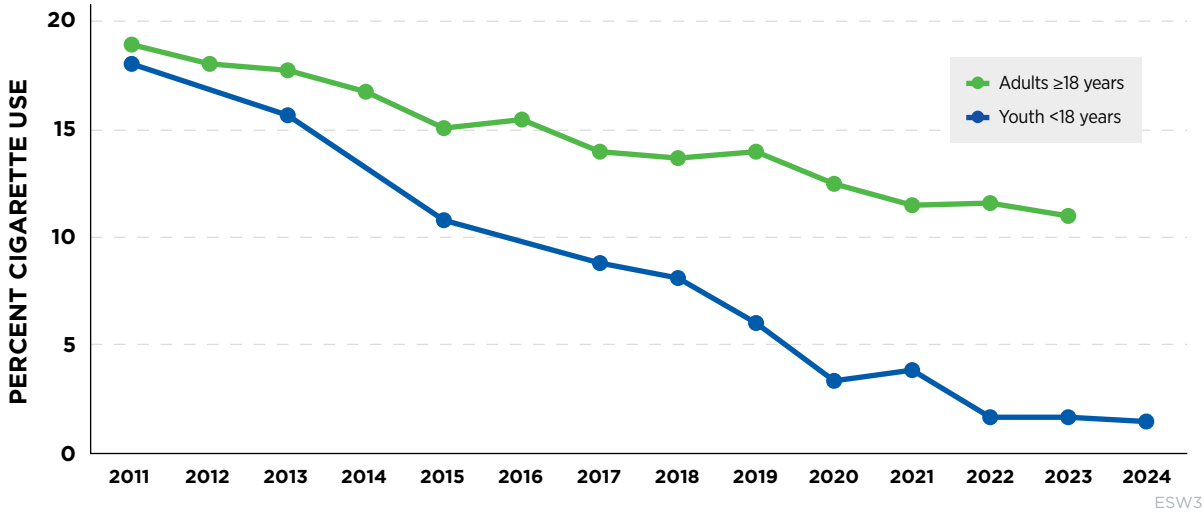
Advances in basic, translational, and clinical research and population sciences have broadened our understanding of factors that contribute to an individual's risk of developing cancer. Approximately 40 percent of all cancers in the United States are attributable to modifiable causes. These risk factors include tobacco use, excess body weight, physical inactivity, excess exposure to ultraviolet (UV) radiation, alcohol consumption, environmental factors, and cancer-causing pathogenic infections.

Between 1975 and 2020, approximately 5.94 million cancer deaths were averted due to public health interventions focused on tobacco control, national screening programs, and vaccination initiatives. While smoking rates have declined significantly, the rising prevalence of other risk factors, particularly obesity among children and adults as well as alcohol consumption, remains a significant public health concern. If left unaddressed, these trends can jeopardize the progress made against cancer over the last 50 years.

In the United States, the prevalence of obesity among adults was 40.3 percent between 2021 and 2023. There is emerging evidence that weight loss interventions, such as bariatric surgery and glucagon-like peptide-1 (GLP-1) medications (e.g., Wegovy, Ozempic), reduce the risk of developing obesity-related cancers. When combined with a healthy diet and regular physical activity, these interventions can significantly promote weight loss in individuals with obesity, subsequently lowering the risk of cancers such as liver, colon, pancreatic, esophageal, and gallbladder.

While addressing modifiable risk factors is crucial in reducing the risk of developing certain cancers, psychosocial and systemic factors cannot be overlooked. Psychosocial factors, such as stress, have been linked to increased cancer risk. Stress may directly contribute to cancer development by promoting

Cigarette Use Among US Adults and Youth (2011–2024)



inflammation, disrupting hormone balance, and impairing immune function. It may also indirectly raise cancer risk by encouraging unhealthy behaviors such as smoking, excessive alcohol consumption, and poor dietary habits.

Environmental risk factors, which are often unavoidable, are present in the air, water, and food, and can contribute to cancer development. The rising incidence of lung cancer among individuals who have never smoked is increasingly linked to exposure to carcinogens found in air pollution. Another class of environmental carcinogens that is of increasing concern is per- and poly- fluoroalkyl substances (PFAS), which are a group of endocrine-disrupting chemicals used in household products, food packaging, textiles, and flame retardants. PFAS persist in the environment, increasing long-term exposure to these harmful substances. Exposure to PFAS has been linked to an increased risk for cancers of the kidney, liver, and thyroid.

In recent years, wildfires in the Western United States and Canada have grown more frequent and severe due to climate change. Individuals at greatest risk of exposures to the carcinogenic byproducts from wildfire suppression are those living near affected areas as well as firefighters or first responders involved in containment efforts. Exposure to these carcinogens increases the risk for multiple cancers including lung cancer and gliomas.

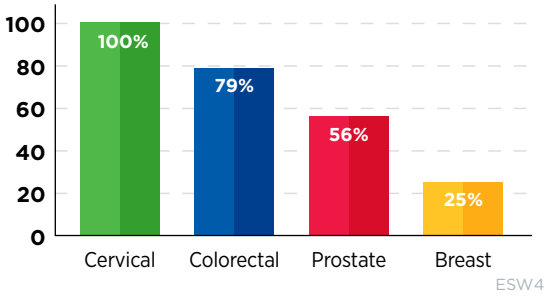
As our understanding of cancer risk factors evolve, it is essential to invest in collaborative and translational research that builds upon existing knowledge and accelerates the pace of progress in cancer prevention and control. Additionally, lawmakers should prioritize developing policies that protect all segments of the US population, especially those unable to avoid risk factors due to their geographic location or occupation.

Cancer Screening for Early Detection

Cancer screening means checking for signs of cancer or for cells that might become cancerous in people who have no symptoms of the disease. The goal is to find cancer early, when it is most treatable and the chances of better outcomes are the highest. A growing body of evidence shows that screening not only saves lives, but it also helps reduce the overall burden of cancer across the population.

In the United States, experts on the US Preventive Services Task Force (USPSTF) develop guidelines for individuals at an average risk of developing cancers of the breast, cervix, colon and rectum, and prostate, as well as for individuals at a higher risk of developing lung cancer. These recommendations are based on several factors, including a person's age, sex, family history, lifestyle, and environmental exposures. The USPSTF regularly reviews new scientific evidence and, if needed, revises these screening guidelines.

Proportion of Total Cancer Deaths Averted Due to Screening and Removal of Precancerous Lesions (1975–2020)



Screening is a process that also involves follow-up care if something abnormal is detected. Unfortunately, many people, especially those in medically underserved communities, face barriers that prevent them from getting screened or receiving timely follow-up care. These barriers include lack of insurance, limited access to quality care, mistrust of the medical system, experiences of discrimination, and poor communication with providers.

Researchers have identified proven strategies that are helping more people get screened, such as incorporating patient navigation, using electronic health records to send reminders, making it easier to access testing, and building trust through approaches that are tailored to the needs of different communities.

Early detection of cancer is a very active area of research, with growing excitement around new technologies. During the 12 months covered by this report, FDA has approved several devices and software that use artificial intelligence (AI) to detect cancer earlier and more accurately. Another area of rapid progress is the development of minimally invasive screening approaches, with FDA approvals of a blood-based and a stool-based test for colorectal cancer screening, and of a self-collection device that enables at-home sample collection for cervical cancer screening. Innovations in imaging, as well as a better understanding of genetic alterations that increase a person's cancer risk, are also improving early detection of cancer. These advances hold promise, but experts emphasize the need for long-term studies to ensure these tools improve outcomes without causing harm or widening existing cancer disparities.

Unifying Cancer Science and Medicine: A Continuum of Innovation for Impact

The dedicated efforts of researchers across the spectrum of cancer science and medicine are driving breakthroughs in clinical care that are improving survival and enhancing quality of life for patients in the United States and worldwide. 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 genetic 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 stories of **Michelle Anderson-Benjamin** (see p. 118), and **Bob Fortin** (see p. 114).

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, and policymakers to remove barriers and promote equitable access to research opportunities.

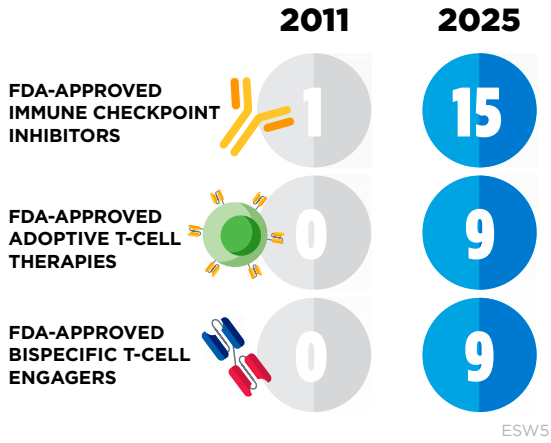
Surgery, radiotherapy, and chemotherapy are three of the five foundational pillars of cancer treatment. While effective, these therapies can have long-term side effects. Ongoing clinical studies are exploring whether less intensive use of these modalities can provide comparable outcomes for some patients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

Fueled by research, 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, 2024 and June 30, 2025, FDA approved 20 new therapeutics for treating various cancer types, one new device for treating lung cancer, and expanded indications for eight previously approved therapies to include new cancer types.

These advances include several groundbreaking immunotherapies. For example, afamitresgene autoleucel, a first-in-class adoptive cell therapy, known as T-cell receptor (TCR) T-cell therapy, is offering new hope to patients with synovial sarcoma, such as **Quinn Johnsen** (see p. 138). A new therapeutic antibody, zolbetuximab-clzb (Vyloy), targeting a novel protein on stomach cancer cells is now benefiting individuals with gastroesophageal cancer, such as **Greg Myers** (see p. 142). These approvals reflect the growing potential of immunotherapy to tackle rare and intractable cancers. The dramatic rise in the use of immune checkpoint inhibitors—immunotherapies that help restore the immune system's ability to recognize and attack cancer cells—further underscores this potential. Since the first *AACR Cancer Progress Report* was released in 2011, the number of FDA-approved ICIs has grown from just one for melanoma to 15 therapies now used to treat more than 20 cancer types.

15 YEARS PROGRESS AGAINST CANCER

Immunotherapy has advanced rapidly, offering patients powerful, personalized treatment options



Equally impressive are the innovative newly approved molecularly targeted therapies that are reshaping and improving cancer care. A new combination regimen comprising avutometinib and defactinib is now providing effective treatment for certain types of ovarian cancer, as seen in the experience of **Mary Catherine Riley** (see p. 120). Patients with low-grade glioma, such as **Alex Hepner** (see p. 126), are benefiting from vorasidenib (Voranigo), the first targeted therapy that inhibits mutated forms of the proteins IDH1 and IDH2 in brain tumors. For patients such as **Dawn Varrati** (see p. 124), diagnosed with the aggressive bile duct cancer cholangiocarcinoma, the approval of zanidatamab-hrii (Ziihera), a new bispecific antibody, has opened new treatment possibilities. These cutting-edge therapies exemplify how deeper biological insights are translating into more precise and effective treatments for patients with difficult-to-treat cancers.

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.

A Decade of Progress: Transformative Advances in Blood Cancer

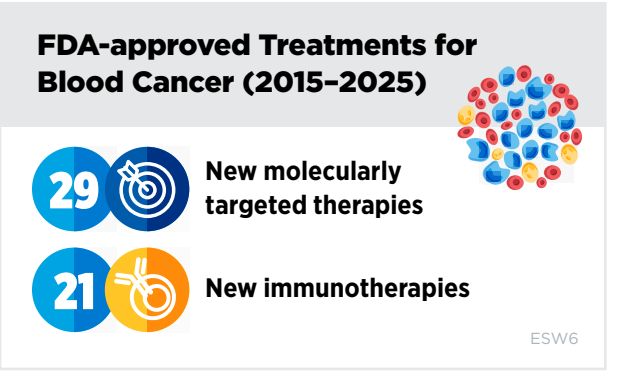
Blood cancers, also known as hematologic malignancies, are a group of cancers that begin in blood-forming tissues of the body, such as the bone marrow. These cancers are broadly categorized as leukemia, lymphoma, and multiple myeloma, and pose a significant public health challenge in the United States and globally. In 2025, an estimated 192,070 new cases will be diagnosed, and 56,110 deaths will occur in the United States from the three most common blood cancer types (leukemia, lymphoma, and multiple myeloma); 1,393,600 new cases and 745,000 deaths are estimated globally.

Thanks to research-driven scientific breakthroughs and technological innovations, death rates from blood cancers have declined significantly, and many people diagnosed today are living longer and fuller lives. As a result, once considered among the most difficult cancers to treat, blood cancers are increasingly becoming manageable or even curable for many patients. As an example, mortality rates for non-Hodgkin lymphoma (NHL)—the most common type of blood cancer in the United States—have declined by 47 percent between 1997 and 2023. As of January 1, 2025, over 1.67 million survivors of blood cancers were living in the United States.

Deeper understanding of molecular underpinnings of blood cancers, propelled by significant federal investments in discovery science, led to the development and approval of one of the first molecularly targeted therapeutics, imatinib (Gleevec), for the treatment of chronic myelogenous leukemia (CML). Imatinib not only transformed clinical care of patients with CML, but it also catalyzed a revolution in precision medicine that has significantly improved health outcomes for millions of patients with cancer. A remarkable example of progress in blood cancer precision medicine is the recent approval of revumenib, the first menin-targeted therapy, offering a new treatment option for patients with acute myeloid leukemia (AML), such as **John C. (Jack) Moorman** (see p. 160).

Progress against blood cancers has also paved the way for breakthroughs in other areas of medicine. Many treatments originally developed for leukemia or lymphoma are now being evaluated, and in some cases successfully used, for solid tumors. Some discoveries in blood cancers have even had applications in treating autoimmune diseases and rare genetic disorders.

Despite rapid strides against blood cancers over the past decade, advances in precision medicine are not benefiting everyone equally. In the United States, certain populations, such as residents of rural areas and medically underserved populations, still face significant barriers to accessing the latest treatments. Similarly, in many low- and middle-income countries, people with blood cancers often go undiagnosed, untreated, or they receive care that is outdated due to lack of resources and infrastructure.



Although challenges such as access to cutting-edge treatments remain, the pace of progress against blood cancers has never been more rapid. Researchers are innovating clinical trial design to inform clinical decisions, such as whether to monitor or intercept blood cancer and whether a patient would benefit from stopping the treatment. These innovations are leading the way to develop similar approaches for solid tumors. Continued federal investment in research and greater collaboration across all sectors are vital to ensure access to quality care and secure a brighter future for all patients with blood cancers.

Supporting Cancer Patients and Survivors

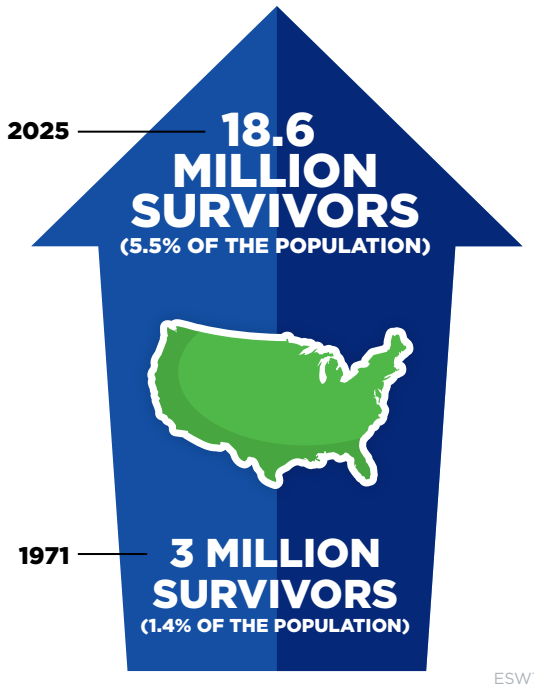
According to NCI, a person is considered a cancer survivor from the time of cancer diagnosis through the balance of their life. Unprecedented advances in cancer treatments over the past decade have led to more patients living longer and fuller lives after a cancer diagnosis. As of January 1, 2025, more than 18.6 million adults and children with a history of cancer were living in the United States, which equates to about 5.5 percent of the population. This is a substantial improvement from 50 years ago, when cancer survivors constituted only 1.4 percent of the US population. The number of cancer survivors is projected to grow to over 22 million by 2035.

Depending on the type and stage of cancer, as well as the age at which an individual is diagnosed, cancer survivorship can encompass a wide range of unique experiences. For example, some people may live cancer free for the remainder of life following successful treatment, while others may manage cancer as a chronic illness requiring ongoing treatment and monitoring, experience persistent side effects, or face a recurrence or a new cancer diagnosis. Understanding and addressing the physical, psychosocial, and financial challenges

faced by cancer survivors, supporting their quality of life, and ensuring that care is accessible and equitable are important priorities in cancer survivorship research.

Research has shown that maintaining a healthy diet, staying physically active, limiting alcohol intake, and quitting smoking can help mitigate the physical challenges associated with a cancer diagnosis. Researchers are also using other evidence-based strategies, including palliative care, behavioral health interventions, patient-reported outcomes, and patient navigation, to help reduce the adverse impact of a cancer diagnosis on the physical and emotional health of cancer survivors. Understanding the challenges experienced by cancer survivors, as well as how to reduce or eliminate them, is an active and continually evolving area of research.

Challenges experienced by patients and survivors of cancer also extend to friends and family members who are often informal caregivers. It is estimated that over four million caregivers are caring for an adult cancer patient in the United States. These caregivers support cancer survivors in various ways, such as arranging transportation for medical appointments, helping with day-to-day activities, coordinating care, and providing emotional support. While fulfilling the caregiving role, this can be physically, emotionally, and financially demanding. Caregivers are at an increased risk for psychological distress, and many face disruptions to their employment, education, or personal well-being. As the number of cancer survivors continues to grow, advancing survivorship and caregiver support through research, policy, and practice is essential to improving outcomes for all those affected by cancer.



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"I think the field of cancer science and medicine is moving incredibly fast, and we must be at the cutting edge to ensure benefit for our patients. Artificial intelligence [AI] will help us learn from massive amounts of data to recognize patterns more efficiently. Liquid biopsy is a game changer, allowing us to detect cancer at a molecular level and intervene before it returns. And with more targeted, less toxic therapies, we are entering an era where even the most difficult cancers may become manageable."

Lillian L. Siu, MD, FAACR, FRCPC
AACR President, 2025–2026

Envisioning the Future of Cancer Science and Medicine

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.

Technological and therapeutic advances against cancer and their impact on saving and improving lives of patients are a source of great optimism for cancer researchers, including **AACR President, 2025–2026, Lillian L. Siu, MD, FAACR, FRCPC** (see p. 196).

Emerging technologies are driving progress in cancer research by enabling researchers to investigate tumors with greater precision and gain deeper biological insights. AI is transforming cancer research and patient care by enabling faster, more accurate, and personalized approaches across the cancer continuum. AI is now being applied to analyze histopathology images, identify genomic alterations, discover new drug candidates, improve early detection, streamline drug development, and support clinical decision-making.

CRISPR gene editing tools are advancing cancer research and drug development by enabling disease modeling, high-

throughput drug screening, and the development of new therapeutic strategies. CRISPR-based systems are being used to uncover which mutations drive tumor development, identify vulnerabilities in cancer cells, and design personalized treatment approaches.

Another rapidly advancing technology is liquid biopsy, the analysis of blood or other body fluids for tumor-derived material routinely shed during cancer development and treatment. 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.

Emerging therapies, many of which are still the focus of ongoing research, are advancing the frontiers of precision oncology and are poised to transform the future of cancer care. One exciting area is the development of cancer vaccines that either prevent cancer in high-risk individuals or treat existing disease by training the immune system to recognize and attack tumor-specific targets. Preventive cancer vaccines that target the molecular characteristics of cancer hold great promise to reduce cancer risk, lessen the burden of ongoing surveillance, and reshape how we approach cancer prevention. Therapeutic cancer vaccines are designed to activate a patient's immune system after cancer has developed, often by targeting unique proteins found on cancer cells.

Another promising class of therapies is radiopharmaceuticals, including radioligand therapies (RLTs), which deliver cytotoxic radiation directly to cancer cells. RLTs combine a radioactive compound with a targeting agent that binds to specific proteins expressed on the surface of cancer cells, enabling the delivery of high-energy radiation to tumors while sparing surrounding healthy tissues and offering a highly localized, tumor-specific radiotherapy approach.

Advancing Cancer Science and Medicine Through Evidence-based Policies

Federal government policies play a critical role in advancing cancer research, developing safe and effective new treatments, improving patient outcomes, and supporting the next generation of researchers and physician-scientists. Sustained investments over decades in vitally important agencies such as NIH, NCI, FDA, and CDC have led to significant progress across the cancer care continuum—from improvements in prevention and early detection to breakthroughs in treatment and survivorship. These agencies support the discovery of lifesaving therapies, strengthen the clinical trial infrastructure, train the scientific workforce, and expand access to cancer screening and care. Federal funding of medical research also spurs our nation's economy. Every $1 in NIH funding returns $2.56 in economic activity.

The proposed $17.97 billion reduction to NIH funding in the administration's FY 2026 budget would severely undermine this progress and jeopardize the nation's leadership in medical research. Such drastic reductions would stall scientific discovery, limit access to promising new therapies for patients such as **Richard Schlueter** (see p. 212), and discourage the next generation of researchers at a critical time.

Therefore, AACR was thrilled that the Senate Appropriations Committee voted in a bipartisan manner on July 31, 2025, to advance the FY 2026 Labor, Health and Human Services, and Education (Labor-HHS-Ed) Appropriations Subcommittee bill and provide $47.2 billion for NIH and $7.374 billion for NCI, reflecting funding increases in these agencies of $400 million and $150 million, respectively.

According to a recent poll, 77 percent of Americans oppose reducing federal funding for medical research. By rejecting the administration's proposed cuts to NIH, the US Senate aligned with the public's priorities, recognizing the vital role of NIH in accelerating progress against cancer and countless other diseases affecting millions of Americans. These bipartisan actions are essential to protecting our nation's scientific enterprise, preserving public trust in science, and sustaining the lifesaving research on which patients and families depend.

AACR Call to Action

For more than 50 years, bipartisan investment in medical research has driven historic progress against cancer, delivering earlier detection, better treatments, and more time for millions of patients and families. That progress is now in jeopardy. Prolonged funding uncertainty and administrative and political interference are weakening cancer research, undermining scientific integrity, and eroding the infrastructure that turns discovery into patient care.

Promising signs of bipartisan resolve in Congress show that this damage can be stopped and progress restored. The fight against cancer is at a decisive moment, and lawmakers have the power to ensure that promising science moves forward, discoveries reach patients, and hope for a future without cancer is not lost.

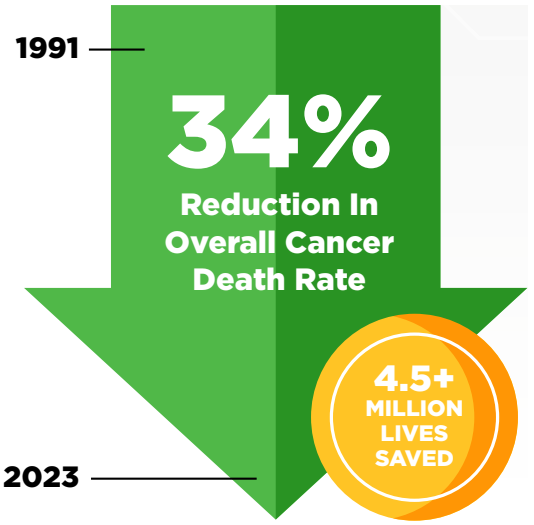
AACR urges Congress to take immediate action to:

- Restart clinical trials and restore canceled research grants to ensure that patients are not turned away from lifesaving studies and that promising science is not lost at a critical stage.

- Support the federal research infrastructure to repair the damage caused by mass reductions in workforce, frozen contracts, and suspended peer review. Discovery has stalled, and scientific capacity is breaking down.
- Protect public health programs that prevent cancer to avoid losing ground on screening, HPV vaccination, tobacco cessation, and early interventions. These efforts save lives.
- Ensure that new treatments reach patients without delay to prevent promising therapies from being trapped in bureaucratic limbo while families wait for help that may come too late.
- Foster early-career and early-stage scientists and stabilize research careers to stop the exodus of postdoctoral researchers and junior investigators who are abandoning science or being recruited overseas. When they leave, they take future cures with them.
- Defend the independence and integrity of science by reversing the August executive order that politicizes federal grantmaking, thus restoring safeguards that keep research free from political interference and ensuring that grantmaking, peer review, and public policies are guided by scientific evidence rather than ideology.
- Reassert America's global leadership in medical innovation to preserve decades of progress and prevent other nations from overtaking the United States in the race for the next generation of cures.
- Provide no less than $51.303 billion for NIH and $7.934 billion for NCI in fiscal year 2026 to sustain the scientific workforce, power new breakthroughs against cancer and other human diseases, and uphold a national commitment to the patients and families who are relying on lifesaving progress.

Cancer touches every family, every community, and every generation. At this defining moment, Congress owes it to every patient, every survivor, and every family to protect the progress we have made and deliver on the promise of a future without cancer.

Snapshot of a Year of Progress



Between July 1, 2024, and June 30, 2025, the US Food and Drug Administration (FDA) approved:

- 20 — **New anticancer therapeutics**, which are now benefiting patients with various types of cancer
- 8 — **Previously approved anticancer therapeutics** for treating new types of cancer
- 2 — **New devices,** one for treating lung cancer and one for cervical cancer screening
- 2 — **Minimally invasive tests** for colorectal cancer screening
- AI — **Several artificial intelligence (AI)–based tools** to improve early detection and diagnosis of cancers

Research continues to advance immunotherapy, leading to:

- The first T-cell receptor (TCR) T-cell therapy that is benefiting patients with synovial sarcoma, such as **Quinn Johnsen** (see p. 138).
- A new therapeutic antibody targeting a novel protein on stomach cancer cells that is benefiting individuals with gastroesophageal cancer, such as **Greg Myers** (see p. 142).
- The first approval of an immune checkpoint inhibitor for the treatment of patients with anal cancer.

Research continues to power precision medicine, leading to:

- A new combination regimen that is providing new hope to patients with ovarian cancer, such as **Mary Catherine Riley** (see p. 120).
- The first approval of an IDH-targeted therapy for brain tumors that is bringing new hope to young adult patients, such as **Alex Hepner** (see p. 126), who are commonly affected by this mutation.
- A new antibody–drug conjugate that is benefiting patients with breast cancer, such as **Michelle Anderson-Benjamin** (see p. 118), as well as those with lung cancer.

Modifiable risk factors such as:

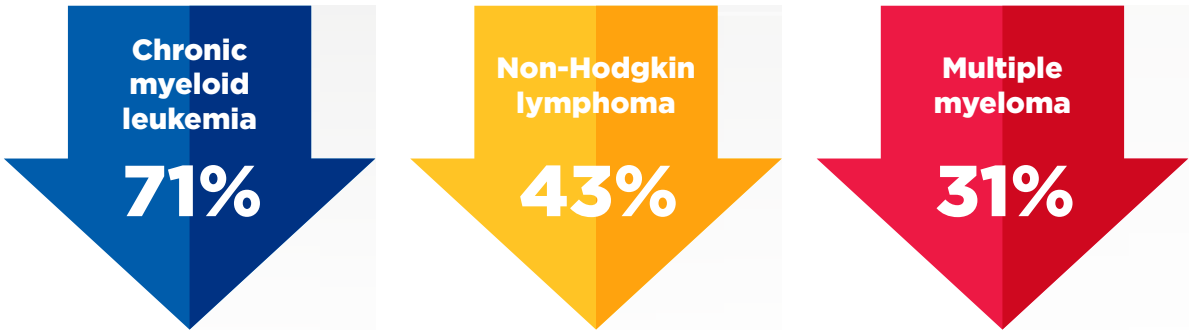
- Cigarette Smoking
- Excess Body Weight
- Alcohol Consumption
- UV Radiation Exposure
- Poor Diet
- Pathogenic Infections
- Physical Inactivity

ARE ATTRIBUTABLE TO:

40% **Of all cancer cases in the US**

41% **Of all cancer cases and deaths globally**

Mortality Reduction in the United States for Selected Blood Cancers (1991–2023)



Over the past decade, FDA has approved numerous innovative therapies for the treatment of blood cancers, including:

29 **New molecularly targeted therapies**, including **4 antibody–drug conjugates (ADCs)**, one of the most exciting and rapidly advancing classes of agents driving precision medicine

21 **New immunotherapeutics**, including **7 CAR T-cell therapies** and **8 bispecific T-cell engagers (BiTEs)**, two of the most promising frontiers in cancer immunotherapy

In just the 12 months covered in this report, FDA approved:

- The **first menin-targeted therapy** for patients with acute myeloid leukemia (AML) such as **John C. (Jack) Moorman** (see p. 160), with cancers harboring specific genetic alterations.
- A **novel cytotoxic fusion protein** for the treatment of cutaneous T-cell lymphoma, a rare form of non-Hodgkin lymphoma.
- A **new CAR T-cell therapy** for patients with acute lymphocytic leukemia (ALL), expanding options for this aggressive cancer.

AACR urges Congress to take immediate action to:

- **RESTART** clinical trials and restore canceled research grants
- **SUPPORT** the federal research infrastructure
- **PROTECT** public health programs that prevent cancer
- **ENSURE** that new treatments reach patients without delay
- **FOSTER** early-career and early-stage scientists and stabilize research careers
- **DEFEND** the independence and integrity of science
- **REASSERT** America's global leadership in medical innovation
- **PROVIDE** no less than $51.303 billion for NIH and $7.934 billion for NCI in fiscal year 2026

Cancer in 2025

IN THIS SECTION, YOU WILL LEARN:

- In the United States (US), the overall cancer death rate has been steadily declining since the 1990s, translating into more than 4.5 million cancer deaths avoided between 1991 and 2023.
- The decline in overall US cancer death rate is attributable to reduction in smoking rates, as well as improvements in treatment and early detection of certain cancers.
- Approximately 18.6 million cancer survivors were living in the US as of January 1, 2025.
- Progress has not been equal against all cancer types or all stages of a given cancer type.
- Many segments of the US population experience stark inequities in the cancer burden; these inequities are largely driven by structural and social factors.
- The economic burden of cancer on individuals and the US health care systems is expected to rise in the coming decades, highlighting the urgent need for more research and increased federal support for medical science and public health.
- It is imperative that all stakeholders work together to implement evidence-based interventions, including public policies that guarantee equitable access to quality health care for all patients.

Research: Driving Progress Against Cancer

Research is the cornerstone of progress against the collection of diseases we call cancer. It drives every basic science discovery, accelerates every clinical breakthrough, and informs public policies designed to improve health outcomes, ultimately leading to better survival and 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 Science and Medicine**, p. 194), 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).

Remarkable progress against cancer—in particular, improvements in early detection, diagnosis, treatment, and risk reduction—has led to a steady decline in US cancer death rates over the past several decades. Between 1991 and 2023, the age-adjusted overall cancer mortality rate declined by 34 percent, a reduction that translates into averting more than 4.5 million deaths from cancer (2). The steady progress in reducing cancer mortality is largely attributable to reduced smoking rates and subsequent declines in lung cancer mortality, declines that have accelerated in recent years due to advances in treatment and early detection (see **Matching Therapies to the Molecular Drivers of Lung Cancer**, p. 110) (2).

Declines in death rates for colorectal cancer and female breast cancer have also contributed to the progress in reducing overall

SIDEBAR 1

The Medical Research Community: Driving Progress Together

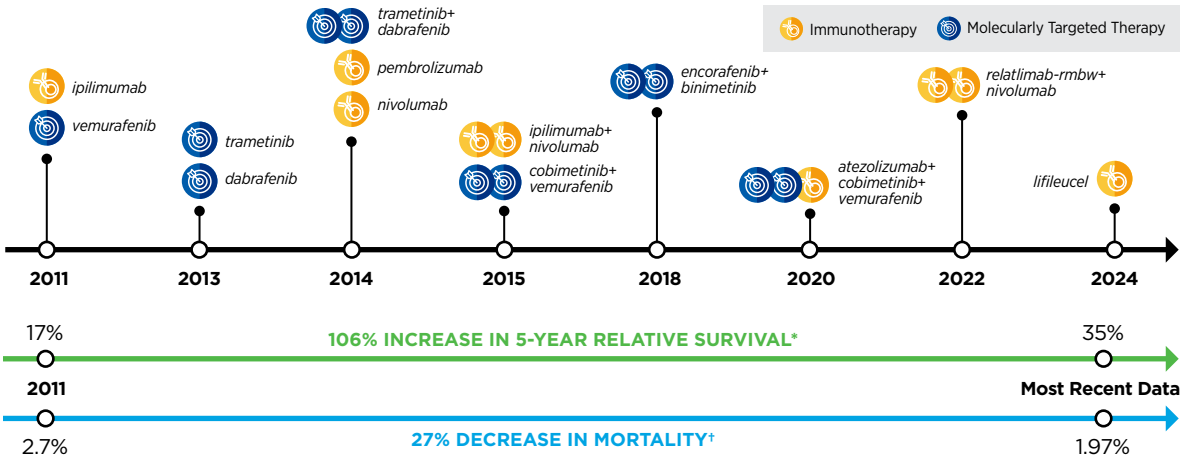
Progress against cancer can be accelerated when all stakeholders who are dedicated to fundamentally changing the burden of cancer work together. Further increasing collaborations will amplify future breakthroughs. The key stakeholders in medical research include:

Adapted from (1).

US cancer mortality (2). According to a recent analysis, US breast cancer mortality declined by 44 percent, averting more than 517,000 deaths between 1989 and 2022, owing to advances in screening mammography and personalized treatments (see **Cancer Screening for Early Detection**, p. 71) (2,3). Similarly, the death rate for colorectal cancer declined by 49 percent between 1990 and 2023 (4). However, this progress has been limited to older adults, as colorectal cancer death rates among

FIGURE 1

Increasing Innovative Treatment Options for Advanced Melanoma



*5-year survival estimates based on cases diagnosed from 2005 to 2011 versus 2015 to 2021.
†Death rate per 100,000 people.

Since 2011, the FDA approved numerous immunotherapies and molecularly targeted therapies for advanced melanoma, reflecting major breakthroughs in cancer research. These advances have revolutionized the therapeutic landscape for advanced melanoma, leading to dramatic improvements in survival and fewer melanoma-related deaths.

This timeline focuses on systemic treatments for metastatic melanoma of the skin; other therapeutics have been approved for the treatment of localized lesions or for other rarer forms of melanomas. For example, in January 2022, FDA approved tebentafusp (Kimmtrak) for the treatment of certain patients with uveal melanoma, an aggressive cancer of the eye.

Data from: NCI Surveillance, Epidemiology, and End Results Program.

those diagnosed before age 50 increased by approximately 14 percent between 1990 and 2023 (4).

Breakthroughs across the spectrum of cancer science and medicine have led to unprecedented progress against aggressive cancers once considered intractable. Research-driven advances in treatment have resulted in a steady decline in death rates for leukemia, melanoma, and kidney cancer, despite increasing incidence of these cancers (2).

For example, groundbreaking basic research in the 1960s through 1980s that identified the mechanistic underpinnings of chronic myeloid leukemia (CML), a cancer of the blood and bone marrow, propelled the development of a cascade of new treatments for CML that have drastically improved outcomes for these patients (see **Leukemias**, p. 145) (5). As a result, the 5-year relative survival rate for CML has more than tripled, from 22 percent in the mid-1970s to 70 percent among individuals diagnosed between 2015 and 2021 (4,6).

More recently, advances in molecularly targeted therapies and immunotherapies have transformed clinical care for several previously difficult-to-treat cancers, including metastatic melanoma (see **Figure 1**, p. 16), lung cancer (see **Matching**

Average Annual Decline in US Death Rates for Selected Cancers (2011–2023)

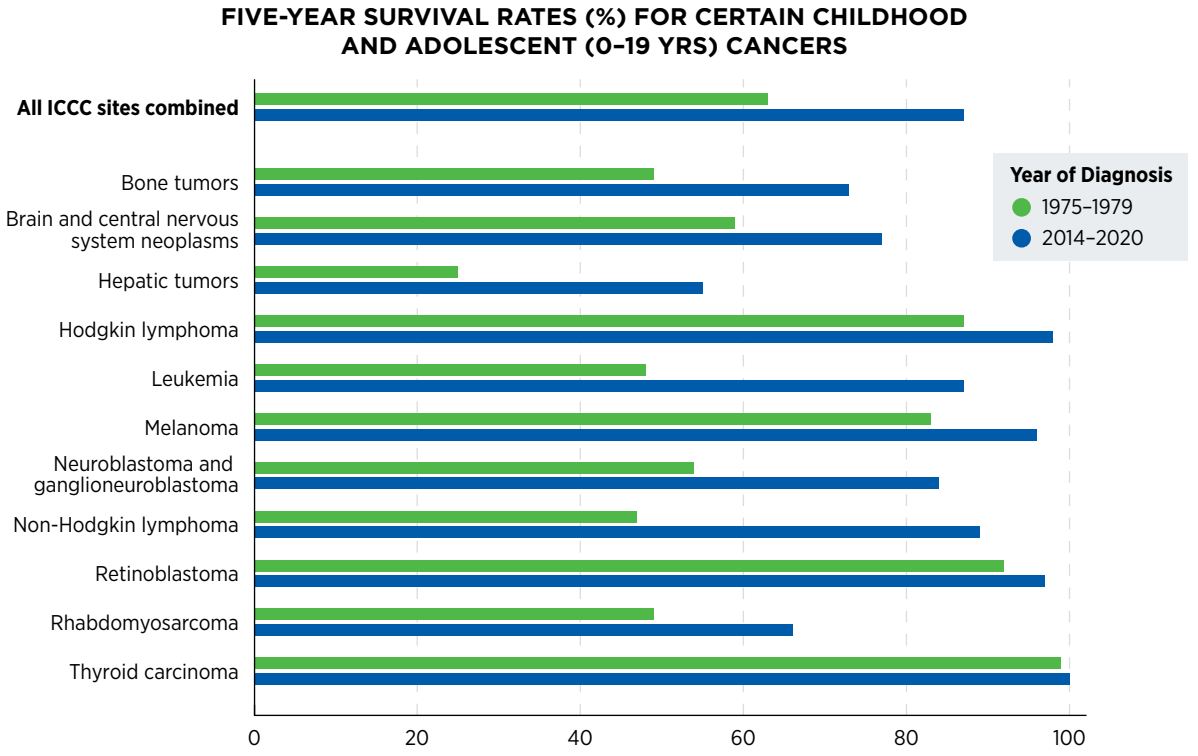
SITE	PERCENT CHANGE
Lung	3.9%
Colorectal	1.5%
Female Breast	1.2%
Prostate	0.7%

Source: (4).

W1

FIGURE 2

Progress Against Cancer in Children and Adolescents



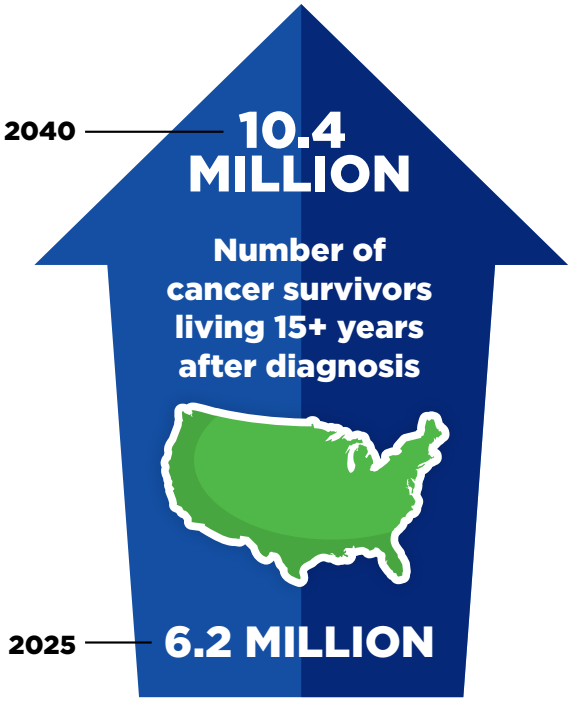
Five-year relative survival rates for the US children and adolescents (ages 0 to 19) who were diagnosed with cancer from 2014 to 2020 were substantially higher compared to those diagnosed from 1975 to 1979. Childhood cancers are classified using the International Classification of Childhood Cancer (ICCC). Improvement in the 5-year relative survival rate was observed for all cancers combined as well as for several individual cancer types.

Therapies to the Molecular Drivers of Lung Cancer, p. 110), kidney cancer, and certain types of breast cancer. For example, the immunotherapy pembrolizumab (Keytruda) was recently shown to be the first postsurgical treatment to extend survival in patients with early-stage kidney cancer (7).

Among the major advances made across the clinical cancer care continuum from July 1, 2024, to June 30, 2025, are 20 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 eight previously approved anticancer therapeutics and one cancer treatment device; two new early detection screening tests, including the first liquid biopsy test and a next-generation multitarget stool DNA test for colorectal cancer screening; a device for at-home sample collection for cervical cancer screening; and a wearable device that uses low-intensity electrical fields to slow the growth of lung cancer cells. 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—as well as those highlighted in past 14 editions of this annual report—are helping more children and adults live longer, fuller lives following a cancer diagnosis, with fewer treatment-related side effects. The 5-year relative survival rate for all cancers combined has increased from 49 percent for those diagnosed between 1975 and 1977 to 70 percent among those diagnosed between 2015 and 2021 (2,4). 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 rates increased from 58 percent to 85 percent in children and from 68 percent to 87 percent in adolescents over the same time period (see **Figure 2**, p. 17) (2,8).

In 2011, when the inaugural *AACR Cancer Progress Report* was released, there were an estimated 12 million cancer survivors living in the United States. As of January 1, 2025, the number of



Sources: (9,10). W2

people living with a history of cancer had grown to 18.6 million, representing approximately 5.5 percent of the US population (9). This reflects a nearly four-fold increase compared to 50 years ago, when cancer survivors made up only 1.4 percent of the US population. The number of cancer survivors is projected to grow to over 22 million by 2035 (9).

Thanks to remarkable advances in cancer research, cancer survivors are now living years, even decades, beyond their initial diagnosis. As of 2025, nearly 50 percent of US cancer survivors have lived 10 years or more since their cancer diagnosis, and 22 percent have lived 20 years or more (9). Moreover, nearly 80 percent of US cancer survivors are age 60 or older, and this proportion is expected to increase with continued advances in treatment and the aging of the population (9). As the population of cancer survivors grows, prioritizing research that addresses their evolving needs must remain a critical focus for US medicine and public health (see **Supporting Cancer Patients and Survivors**, p. 177).

Cancer: An Ongoing Challenge

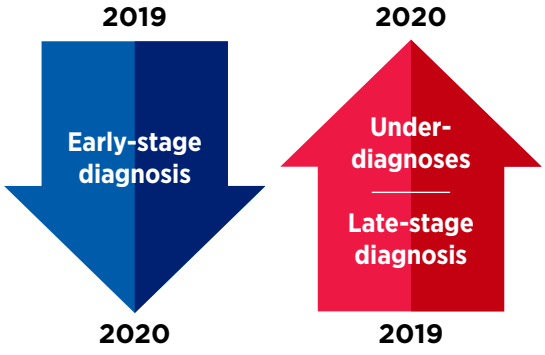
While substantial progress has been made against cancer, the disease continues to be an enormous public health challenge in the United States and around the world. In 2025, an estimated 2,041,910 new cancer cases will be diagnosed and 618,120 people will die from the disease in the United States (see **Table 1**, p. 18). In addition, many population groups in the United States experience disproportionately high rates of cancer incidence and mortality.

TABLE 1

Estimated Burden of Common Types of Cancer in the United States in 2025

	New Cases	Deaths
ALL CANCERS COMBINED	**2,041,910**	**618,120**
Breast	319,750	42,680
Prostate	313,780	35,770
Lung and bronchus	226,650	124,730
Colorectal	154,270	52,900
Melanoma of the skin	104,960	8,430
Bladder	84,870	17,420
Kidney and renal pelvis	80,980	14,510
Non-Hodgkin lymphoma	80,350	19,390
Uterine	67,880	13,250
Pancreatic	67,440	51,980
Thyroid	44,020	2,290
Liver and intrahepatic bile duct	42,240	30,090
Myeloma	36,110	12,030

Sources: (2,4).



The **COVID pandemic caused a marked disruption in cancer diagnoses,** disproportionately affecting racial and ethnic minorities and other medically underserved populations, **exacerbating existing disparities in timely cancer detection**.

Source: (11). W3

SIDEBAR 2

US Population Groups That Experience Cancer Disparities

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

Individuals belonging to certain ancestry, racial or ethnic minority populations

Individuals of low socioeconomic status, including low educational attainment

Individuals who lack or have inadequate health insurance coverage

Individuals belonging to sexual and/or gender minority communities

Individuals with disabilities

Adolescents and young adults

Individuals who are incarcerated

Immigrants, refugees, or asylum seekers

Older adults

Citizens of American Indian/Alaska Native Tribal Nations

Residents in certain geographic locations, including rural areas, or of certain types of neighborhoods, such as those with low access to resources

Inequities in the Burden of Cancer in the United States

Despite overall progress against cancer, significant disparities persist among certain population groups in the United States, across the cancer continuum, linked to structural and socioeconomic disadvantages. Because of a long history of structural inequities and systemic injustices, certain segments of the US population continue to shoulder a disproportionate burden of adverse health conditions, including cancer. These unequal burdens have led researchers and public health experts to closely study cancer disparities.

Cancer disparities are one of the most pressing public health challenges in the United States. The National Cancer Institute (NCI) defines cancer disparities as adverse differences in cancer-related measures, such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and cancer stage at diagnosis, that exist among certain population groups (see **Sidebar 2**, p. 19).

The *AACR Cancer Disparities Progress Report 2024* (12) highlights the disproportionate burden of cancer among US racial and ethnic minority groups and other medically underserved populations (see **Sidebar 3**, p. 20). As one example, while non-Hispanic (NH) White individuals have the highest overall cancer incidence rate, NH Black individuals had the highest overall cancer mortality rate, followed by American Indian/Alaska Natives (AI/AN). Further, between 2015 and 2021, patients with cancer from all racial and ethnic minority groups had lower 5-year relative survival rates (61.7 to 68.4 percent) than NH White individuals (70.8 percent) (4).

SIDEBAR 3

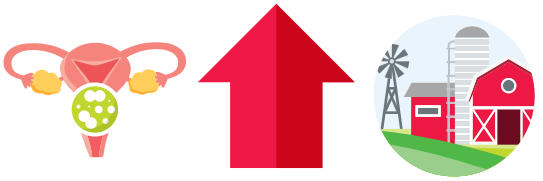
Cancer Inequities in the United States

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 the 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 *AACR Cancer Disparities Progress Report 2024* (12).

16% and 10% higher, 9% lower	Between 2018 and 2022, cancer death rates were 16 percent higher among Black men compared to White men. Black women experienced 10 percent higher cancer mortality compared to White women, despite having a 9 percent lower incidence rate (13).
28% increased risk	Black pediatric cancer patients have a 28 percent increased risk of death compared to White pediatric cancer patients (14).
1.10-, 1.34-, and 1.62-fold higher	Among patients diagnosed with non-Hodgkin lymphoma, the risk of death was 1.10-, 1.34-, and 1.62-fold higher in East Asian, Southeast Asian, and Native Hawaiian or Other Pacific Islander patients, respectively, compared to non-Hispanic White patients (15).
19% vs. 32%	From 2014 to 2018, 5-year survival for stomach cancer was 19 percent and 32 percent among American Indian/Alaska Native and non-Hispanic White individuals, respectively (16).
2-fold higher	Lesbians have a nearly 2-fold higher incidence rate of thyroid cancer, basal cell carcinoma, and non-Hodgkin lymphoma compared to straight women (17).
2X below	In the United States, geographic areas with higher proportions of families living 2 times below the federal poverty level have a higher burden of cervical cancer (18).
5.6% and 12.8% higher	From 2017 to 2021, residents of the Appalachian region of the United States had 5.6 percent and 12.8 percent higher incidence and mortality rates, respectively, from all cancers combined than non-Appalachian residents (19).

Research on the science of cancer disparities is revealing significant differences in incidence and mortality across subpopulations within racial and ethnic groups, underscoring the need to disaggregate data within these populations. Striking disparities in cancer burden have been identified within Asian subpopulations and between Native Hawaiian or Other Pacific Islander (NHOPI) and Asian individuals (12). As an example, the risk of death from pancreatic ductal adenocarcinoma was 10 percent and 22 percent higher among East Asians and Pacific Islanders, respectively, compared to South Asians (20). Notably, the US Asian population has ancestry in numerous countries of origin, and the NHOPI population comprises diverse subgroups with distinct variations in historical backgrounds, languages, and cultural traditions. Still, Asian and NHOPI populations continue to be grouped together in cancer epidemiologic data.

Cancer disparities are caused by many overlapping factors at the individual, community, and societal levels. These include aspects like biology, personal behaviors, access to healthy environments, cultural influences, and differences in quality of health care systems, factors that can affect people throughout their lives (22). To help researchers understand and address these influences, the National Institute on Minority Health and Health Disparities developed a framework to guide the study of contributors



Between 2015 and 2019, **cervical cancer incidence and mortality** were 25% and 42% **higher**, respectively, **in rural** counties **compared to urban** counties.

Source: (21).

W4

to adverse health outcomes and health disparities, including those related to cancer (22). This framework emphasizes the importance of addressing both biological drivers and social drivers of health (SDOH) simultaneously, rather than focusing on any one driver in isolation.

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 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 3**, p. 22).

It is important to recognize that patients with intersectional identities—such as individuals from racial and ethnic minority populations living in disadvantaged rural or urban areas—often face multilevel barriers to cancer care that negatively impact screening, diagnosis, treatment, and survivorship. As an example, Black women living in more socially disadvantaged neighborhoods had significantly worse breast cancer survival compared to those living in the least disadvantaged neighborhoods, even after accounting for clinical and individual socioeconomic factors (23). Neighborhood disadvantage is measured using a weighted composite score based on neighborhood-level characteristics, including the proportion of Black residents, individuals living below the federal poverty level, those receiving public assistance, living in female-headed households, unemployed, or under 18 years of age. Higher scores reflect greater levels of disadvantage.

Inadequate access to quality health care is a major social driver of cancer disparities. A recent review of disparities across the lung cancer continuum revealed that individuals who were younger and not eligible for Medicare had lower screening rates; uninsured patients or those with Medicaid were less likely to receive curative surgery; and individuals with Medicaid or no insurance were less likely to utilize novel therapies and enroll in clinical trials (24). Similar patterns have been observed in breast cancer care, in which women with private insurance were significantly more likely to receive molecularly targeted therapy or immunotherapy, treatments associated with better outcomes (25,26).

Cancer disparities affect multiple segments of the US population, making disparities a significant public health concern that requires tailored efforts to better understand and address these inequities (see **Addressing Cancer Disparities and Improving Patient Outcomes**, p. 224). Health equity for all populations can only be achieved through new insights gained from innovative, inclusive, and translational science. This includes basic research using biospecimens from diverse populations; clinical studies with participants from all sociodemographic backgrounds; and health care delivery and implementation research that reflects every community.

Variable Progress Against Different Types of Cancer and Stages of Diagnosis

A significant challenge in cancer science and medicine is the uneven progress against different cancer types and different stages of a given cancer type. This challenge is reflected in the wide variation in 5-year relative survival rates among US cancer patients, depending on both the type of cancer diagnosed and the stage at diagnosis (4).

For example, the overall 5-year relative survival rate is just 13 percent for pancreatic cancer and 6 percent for glioblastoma multiforme (GBM), an aggressive form of brain cancer, in stark contrast with 92 percent for breast cancer and 98 percent for prostate cancer (4). However, when examining stage-specific 5-year survival rates for breast and prostate cancers, striking differences emerge. Individuals diagnosed with localized disease—cancer that is confined to the breast or prostate tissues—have a 5-year relative survival rate of 100 percent, while individuals diagnosed with metastatic disease—disease that has spread to other organs—have a 33 and 38 percent 5-year relative survival rate, respectively.

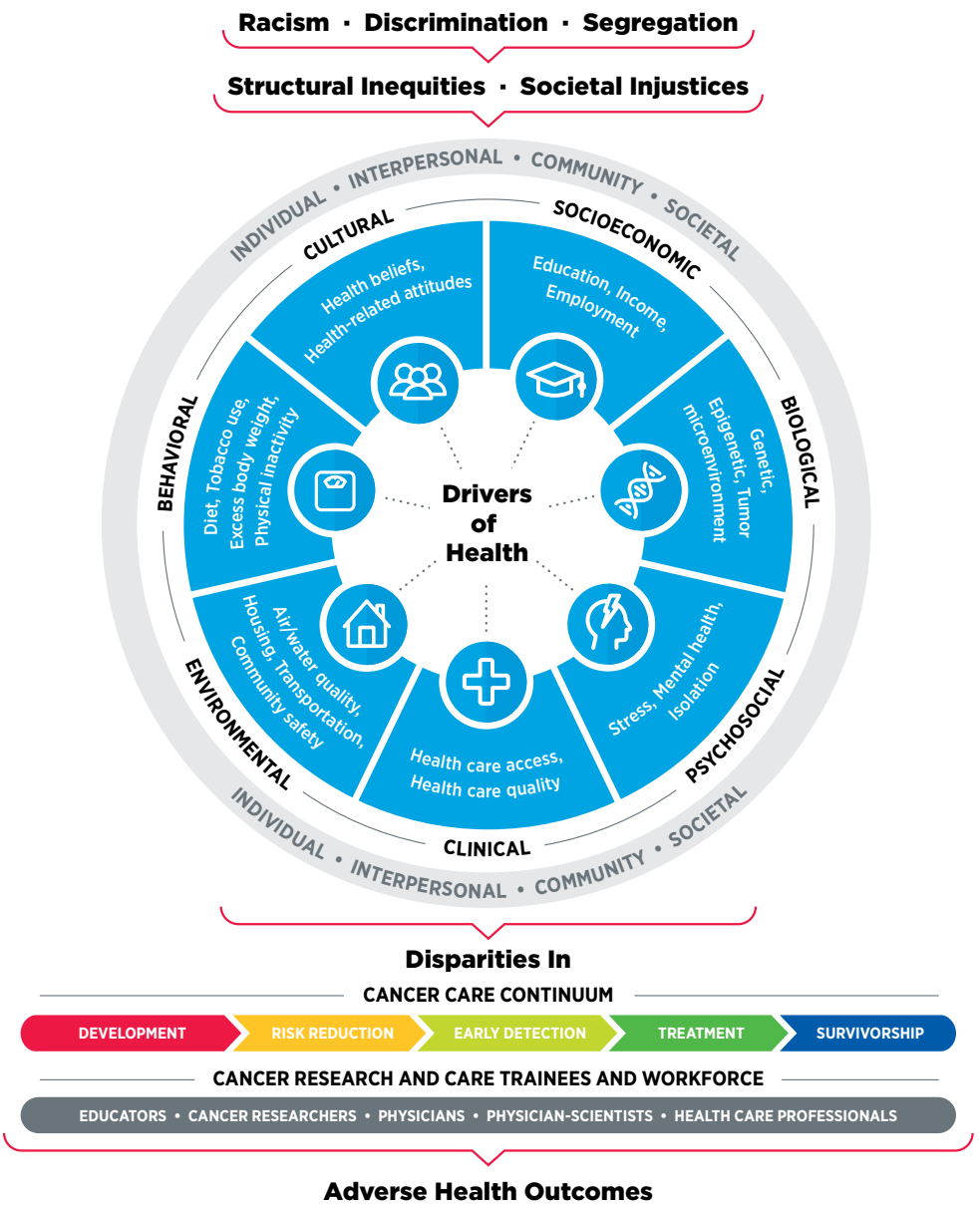
Breast Cancer Death Rate in the United States (2014–2022)

Source: (4).

W5

FIGURE 3

Why Do US Cancer Disparities Exist?



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. The National Cancer Institute 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 get older that can affect their health, well-being, and quality of life. SDOH have a major influence on people's 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 minorities and medically underserved populations. The circle in the figure depicts key drivers of health and how they interconnect both at societal and community levels and at the individual level. 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 racial and ethnic minorities and other underserved populations (shown at the bottom).

Variable progress against different cancer types can be explained in part by disparities in lifesaving therapeutic options that are available for different cancer types. For example, since the release of the first edition of this report in 2011, FDA has approved 20 new molecularly targeted therapeutics, excluding endocrine therapies, and two immunotherapeutics for treating patients with breast cancer. As a result, patients have a deeper selection of therapeutics for the treatment of their disease and breast cancer mortality has been declining steadily.

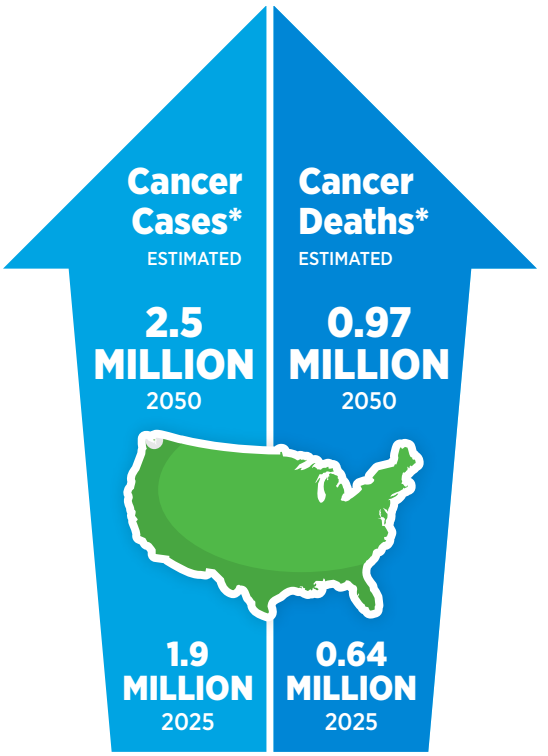
In contrast, treatment options for patients with GBM remain extremely limited. Since the approval of the chemotherapeutic temozolomide nearly 25 years ago, no new anticancer agents have shown promise in improving overall survival. This in part explains why the 5-year relative survival rate for patients with GBM remains at a dismal 6 percent (4).

Developing new and effective tests for the early detection of more cancer types (see **Cancer Screening for Early Detection**, p. 71), in addition to expanding the eligibility for established screening recommendations (27), could also help address the challenges of variable progress between different types of cancer, since the likelihood of a better outcome is much higher when cancer is diagnosed at an early stage, when it is confined to its original location and not spread to distant sites (see **Cancer Screening for Early Detection**, p. 71 and **Figure 12**, p. 72). Additionally, improving and expanding therapeutic options for difficult-to-treat cancers will require intensive research that builds on existing knowledge to uncover the biological drivers of these diseases and inform the development of more effective treatments.

The Growing Population Burden of Cancer

The public health challenge posed by cancer is expected to increase even further in the coming decades unless more effective strategies for prevention, early detection, and treatment are implemented. In the United States, the number of new cancer cases (including non-melanoma skin cancer) diagnosed annually is projected to exceed 3.5 million by 2050—a nearly 40 percent increase from 2025 estimates (28). A major driver of this rise is the growing proportion of older adults in the population, as cancer risk increases significantly with increasing age. In fact, in 2022, 59 percent of all cancer cases occurred in individuals age 65 and older. By 2050, this age group is projected to exceed 82 million people, representing about 23 percent of the total US population. That is a 50 percent increase from 2022, when there were about 58 million older adults, making up roughly 17 percent of the population (29). Notably, cancer cases in the age 65 and older population have remained steady over time, from 61 percent in 1995 to 59 percent in 2021, which could result from the decline in smoking-related cancers in this age group (2).

Also contributing to the projected increase in the number of US cancer cases is the high prevalence of excess body weight,



* Excluding non-melanoma skin cancer.
Source: (30).

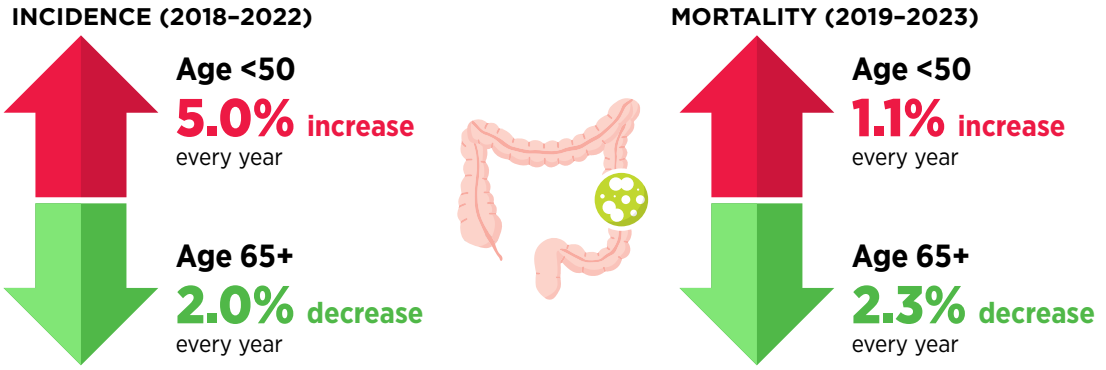
W6

physical inactivity, alcohol consumption, environmental factors, and continued tobacco use (see **Reducing the Risk of Cancer Development**, p. 51) (31,32). For example, although smoking rates have declined precipitously since the 1970s, 11 percent of adults still smoke. However, lung cancer is on the rise in non-smokers (33) and makes up about 16 percent and 10 percent of cases diagnosed in women and men, respectively (34). In 2023, individuals who never smoked accounted for more than 20,000 lung cancer–related deaths (34,35).

A recent review found that lung cancer in people who never smoked exhibits unique tumor characteristics and patterns compared to lung cancers caused by tobacco use. Specifically, these cancers are predominantly adenocarcinomas, the type of cancers that start in mucus-producing cells; occur more frequently in women and individuals of Asian ancestry (36–38); and have many changes in the DNA that researchers can target with specific treatments (see **Understanding the Path to Cancer Development**, p. 29) (35). As lung cancer in people who have never smoked is an emerging public health concern, there is a critical need to identify its 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.

Although overall cancer incidence in the United States has stabilized in recent years, the incidence of certain cancer types, as well as the age- and sex-specific cases of certain cancers, is increasing. For example, the incidence of

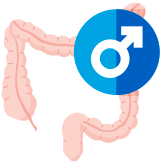
Burden of Colorectal Cancer in the United States



Source: (4).

W7

Among individuals diagnosed with **early-onset colorectal cancer, men were 19% more likely to die** compared to women.



Source: (43).

W8

pancreatic cancer, liver cancer, uterine cancer, and HPV-associated oral cancers (e.g., base of tongue and tonsils) has been rising (39). While the overall incidence of lung cancer is declining in the United States, young (30 to 44 years) and middle-aged (45 to 59 years) women are being diagnosed at a higher rate than men in the same age groups (40). In 2021, lung cancer incidence among individuals ages 65 and younger was slightly higher in women than in men (2). This reverses the historical trend of a higher incidence among men and cannot be attributed to smoking prevalence.

Researchers predict that US individuals born during 1965–1980 (Generation X) will have a higher incidence of cancer as they turn age 60 than those born during 1946–1964 (Baby Boomers) at the same age (41,42). While the exact reasons remain unclear, the increase is thought to be driven by several factors, including a higher prevalence of modifiable risk factors, such as excess body weight, physical inactivity, and exposure to environmental pollutants. Another rising concern among public health experts is the steadily increasing incidence of certain cancer types among individuals younger than 50, a phenomenon referred to as early-onset cancer.

Understanding the reasons behind rising cases of early-onset cancers is an area of intensive research (see **Sidebar 4**, p. 25). From 2010 to 2019, the incidence of 14 cancers—including melanoma, certain lymphomas, and cancers of the cervix, colon, breast, pancreas, stomach, testicles, and uterus—increased in individuals aged 15 to 49 years (44). Notably, early-onset colorectal cancer, which is frequently diagnosed at an advanced stage, has been linked to a significant accumulation of microplastics in the bodies of Generation X individuals, highlighting a potential contributor to risk for this disease (45). One recent study also implicated bacteria, stating that a DNA-damaging toxin produced by certain strains of the bacterium *Escherichia coli* may be a key driver in the rise of early-onset colorectal cancer (46).

To reduce the burden of early-onset colorectal cancer and early-onset breast cancer, the US Preventive Services Task Force (USPSTF), an independent, volunteer panel of experts in prevention and evidence-based medicine, has updated their screening guidelines to recommend starting colorectal and breast cancer screening at an earlier age of 45 years and 40 years, respectively, instead of the previously recommended starting age of 50 years (see **Cancer Screening for Early Detection**, p. 71). Researchers are also evaluating new and improved strategies including genetic testing and other approaches for prevention and early detection of colorectal cancer in the younger population (47,48).

The Global Burden of Cancer

Globally, cancer remains a leading cause of illness and death. According to a recent analysis, there were an estimated 20 million new cancer cases and over 10.3 million deaths from cancer in 2025 (29). An estimated 53.5 million people were living for at least 5 years following a cancer diagnosis. Cancers of the lung, breast, colon and rectum, prostate, and skin (non-melanoma) were the five most frequently diagnosed cancers worldwide in 2022, the most recent year with available data (30,55). Accounting for the most cancer-related deaths globally are cancers of the lung, colon and rectum, liver, stomach, and breast (56).

SIDEBAR 4

What Is Causing the Rise in Early-onset Cancers?

From 2011 to 2019, in the United States, 2,020,829 new cancer cases were diagnosed among individuals ages 15 to 49 years. Although researchers are not sure of the exact reasons why these cancers are rising, several possible causes are under investigation:

Unhealthy diet and the microbiome

Obesity

Chemicals in the environment

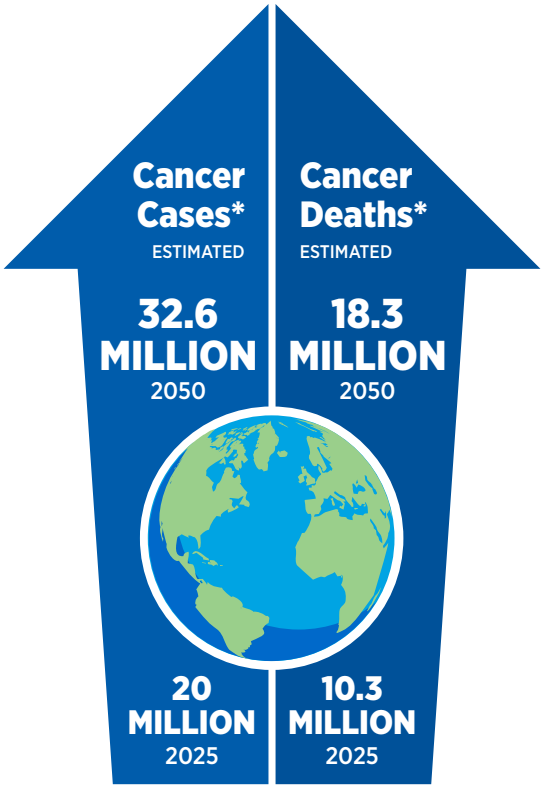
Repeated and long-term use of antibiotics

Alcohol consumption

Sedentary behaviors

Understanding how these risk factors lead to early-onset cancers will help to inform approaches for screening, prevention, and treatment.

Sources: (44,45,49-54).



* Excluding non-melanoma skin cancer.
Source: (30).

W8

Stark disparities in the cancer burden are found among countries with different levels of socioeconomic development. Researchers use metrics, such as the human development index (HDI) or the sociodemographic index (SDI), to identify where countries or geographic areas fall on the spectrum of socioeconomic development. SDI quantification considers income per capita, average years of education, and total fertility rate for citizens younger than 25, whereas HDI measurement considers income per capita, average years of education, and life expectancy at birth.

In low-HDI countries, cancer incidence and mortality are both projected to triple by 2050, in stark contrast to high-HDI countries (28), where rates are expected to remain relatively stable. Additionally, compared to North America, a high-HDI region, Africa, a low-HDI region, has the highest mortality-to-incidence ratios (MIRs) (23.0 percent vs. 67.2 percent, respectively)—a metric that reflects the proportion of individuals who die from cancer relative to the number of new cases diagnosed. A high MIR signals that a larger share of people diagnosed with cancer are dying from it and typically points to limited access to timely diagnosis, effective treatment, and quality of cancer care.

Regional disparities are also observed for specific cancer types. For example, from 1990 to 2021, an annual decline in breast cancer incidence ranging from 0.16 percent to 1.14 percent was observed in high-SDI regions such as Central Asia and Eastern and Western Europe. In contrast, low-SDI regions—including North Africa, the Middle East, and sub-Saharan Africa—experienced annual increases in breast cancer incidence ranging from 2 percent to 3.4 percent (57). Regional differences in breast cancer burden reflect disparities in health care systems and public health efforts. High-SDI regions have seen decreases in burden due to widespread screening, early detection, and advanced therapeutic interventions, whereas low-SDI regions have limited access to screening, diseases diagnosed at advanced stages, and limited, if any, access to advanced therapeutics.

Another emerging concern among public health experts is the rise in cancer diagnoses among adolescents and young adults (AYAs), defined as individuals ages 15 to 39 years. The global

Estimated Increase in Global Burden of Selected Cancers (2022–2050)

SITE	INCIDENCE	MORTALITY
Breast	38.0%	67.9%
Prostate	50.4%	52.3%
Cervical	56.8%	80.7%

Sources: (28,59,60).

W10

burden of AYA cancers is expected to increase by 12 percent from 2022 to 2050 (58). The most common cancers diagnosed in this population include cancers of the breast, thyroid, cervix, blood (leukemia), and colon and rectum, cumulatively accounting for more than 50 percent of all new cases.

As cancer rates rise globally, so does the economic burden of the disease. From 2020 to 2050, the cumulative global economic cost of cancer is projected to reach $25.2 trillion. The cancers contributing most to this burden include those of the trachea, bronchus, and lung; colon and rectum; breast; and liver; as well as leukemia, with the United States and China accounting for the largest share of these costs (61).

To ensure equitable progress against cancer worldwide, global medical research communities must collaborate to share best practices and implement innovative strategies tailored to local needs. Aligning cancer research funding with the global distribution of cancer burden and treatment availability is essential. Public health experts emphasize priorities for low- and middle-income settings, including reducing advanced cancer cases; improving access, affordability, and treatment outcomes; adopting value-based care, for which providers are paid based on patient outcomes and not just volume of patients; advancing implementation research; building research capacity; and leveraging technology (62). Efforts must also focus on preventing and treating infection-related cancers, while increasing investment in cancer surgery and radiotherapy—critical components in the curative treatment of many solid tumors (63,64).

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 medical costs of patient care are just one measure of the financial impact of cancer, and in the United States alone, these costs were estimated to be nearly $209 billion in 2020 (6). Unfortunately, these costs stand in stark contrast to the NCI budget of $6 billion for the same year. Notably, direct medical costs do not include the additional burden of lost productivity due to cancer-related morbidity and mortality (see **Investing in Research to Achieve a Healthier Future**, p. 209). For example, the lifetime productivity losses among US AYAs diagnosed with cancer in 2019 were estimated at $18 billion (65).

Patients with cancer shoulder a large amount of the economic burden associated with cancer care. In 2019, the national economic burden associated with cancer care on patients was estimated to be over $21 billion (66). Of this amount, nearly $5 billion was attributed to time costs—the value of patients' time spent traveling to, waiting for, and receiving care—while an estimated $16.2 billion was attributed to out-of-pocket costs for cancer-related medical expenses (66).

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. A recent analysis estimated that the economic burden of cancer in the United States will reach $5.3 trillion over the next three decades (61). This rising economic toll highlights the urgent need for continued investment in cancer research to accelerate the pace of progress and curb the increasing burden of cancer on patients, families, and the health care system.

As the world's largest public funder of medical research, NIH has long received bipartisan support from US lawmakers. For most of the past decade, consecutive increases in the NIH budget have helped maintain the momentum of progress against cancer and other diseases (see **Sidebar 5**, p. 27). However, in fiscal year (FY) 2024, NIH funding declined for the first time in nearly a decade, breaking a trend of steady growth. NIH funding remained stagnant in FY 2025, with appropriations held flat at FY 2024 levels, marking the second consecutive year without an increase in the agency's budget (see **Figure 25**, p. 211). Meanwhile, the cost of conducting medical research continues to rise, driven by inflation and the increasing complexity of scientific investigations and clinical trials, which often require advanced technologies and highly specialized personnel.

Challenges posed by two consecutive years of stagnant NIH funding were compounded in early 2025, when the administration implemented broad federal budget cuts, resulting in the termination of more than 2,200 research grants and the loss of nearly $3.8 billion in unexpended research funding (79). Training and career development grants have been especially affected, with hundreds of canceled awards intended to support graduate students, postdoctoral fellows, and early-career investigators. These abrupt losses have fueled growing uncertainty within the research community and prompted many US-based scientists to consider opportunities abroad in

SIDEBAR 5

Funding Medical Research. Accelerating Discoveries. Saving Lives.

Decades of federal funding for medical research have transformed cancer care, enabling millions of patients to live longer, healthier lives. These achievements underscore the critical importance of robust federal investment to sustain progress and drive future breakthroughs in the fight against cancer. Federal funding has been pivotal in:

Reducing the Burden of Cancer

- From 1975 to 2020, prevention and screening efforts averted 4.75 million deaths across five major cancer types, including breast, cervical, colorectal, lung, and prostate cancers (67).
- The US cancer mortality rate has declined by 34 percent since 1991, resulting in more than 4.5 million lives saved (2).
- Over the past 40 years, patients with cancer in the United States have gained 14 million years of additional life thanks to federally funded clinical trials (68).
- As of January 1, 2025, approximately 18.6 million cancer survivors were living in the United States.

Leading the World in Cancer Drug Discovery and Innovation

- Between 1990 and 2022, the United States was the first to launch nearly half (45 percent) of all new cancer drugs, leading the world in the approval and introduction of novel anticancer therapies (69).
- NIH-funded research contributed to 354 of the 356 drugs approved by FDA between 2010 and 2019 (70).

Driving Breakthroughs in Precision Medicine

- Discovery of key immune checkpoint proteins and the development of transformative immunotherapies known as immune checkpoint inhibitors (ICIs). Since the FDA approved the first ICI in 2011, a total of 15 ICIs have been approved to treat more than 20 cancer types, including once-deadly diseases like advanced lung cancer, metastatic melanoma, and kidney cancer (71–74).
- Discovery of the genetic driver of chronic myeloid leukemia (CML), which led to the development of imatinib, a breakthrough that transformed CML outcomes—raising the 5-year survival rate from 30 percent in the late 1980s to over 70 percent today—and ushered in the era of precision cancer medicine (4,75).
- Support of the first clinical trials of chimeric antigen receptor (CAR) T-cell therapy (76), which revolutionized treatment for certain blood cancers. This foundational research paved the way for FDA-approved CAR T-cell therapies and continues to guide efforts to expand their use to solid tumors (77).

Fueling the US Economy

- In fiscal year 2024, NIH awarded $36.94 billion to researchers across all 50 states and Washington, DC.
- Every $1 in NIH funding returns $2.56 in economic activity (78).
- This funding supported 407,782 new jobs and generated $94.58 billion in economic activity.

Federal funding fuels **scientific discovery**, drives **economic growth**, and **improves health outcomes** across the United States and around the world. **Continued investment** in medical research is vital to **build on this progress**, accelerate **innovation**, and ultimately achieve the goal of **preventing and curing all cancers**.

countries with more stable funding environments (see **Investing in Research to Achieve a Healthier Future**, p. 209) (80).

Proposed appropriations for FY 2026 suggest continued threats to NIH's capacity to conduct and fund medical research. These funding cuts come at a time when other nations are rapidly expanding their cancer research efforts and have now surpassed the United States in initiating oncology clinical trials (81). Without strong federal support for research, the United States risks losing its position as a global leader in scientific discovery, innovation, and the development of lifesaving cancer treatments (81,82). Beyond institutional disruptions, the impact on public health could be profound. Researchers estimate that proposed NIH funding cuts could result in more than $8 trillion in economic losses over the next 25 years, driven by a decline in new therapies and reduced life expectancy (83).

Discoveries fueled by NIH funding have transformed cancer prevention, detection, and treatment, turning once-fatal diagnoses into manageable conditions, saving millions of lives, and offering hope to millions more. Sustained and predictable federal funding is essential to preserve US leadership in biomedical research, safeguard progress against cancer, support the development of future 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. 227).

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 develops 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.

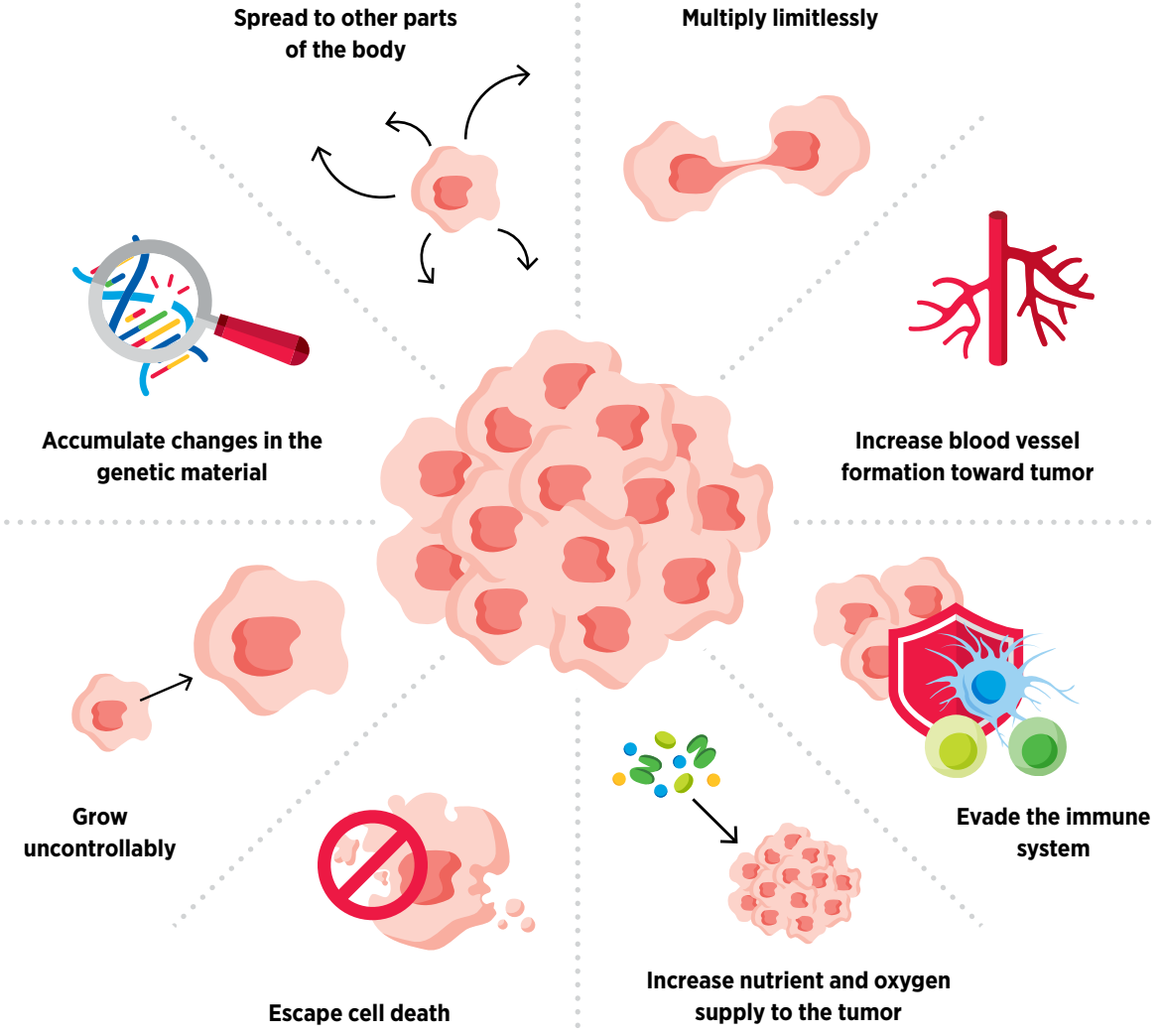
These hallmarks include the ability of cancer cells to multiply unchecked; acquire changes that make their genetic code unstable; ignore signals that stop normal cells from dividing; utilize different metabolic strategies to sustain rapid growth; leave the tissue of origin and spread to other organs; evade the immune system, which typically eliminates abnormal or damaged cells; and increase the supply of nutrients and oxygen to tumors (see **Figure 4**, p. 30) (84,85).

Cancer Development: Generating Knowledge Through Basic Research

Basic research focuses on gaining new knowledge or a deeper understanding of 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. Researchers explore these biological mechanisms using a wide array of experimental models that mimic healthy and disease conditions (see **Sidebar 6**, p. 31). 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

FIGURE 4

Hallmarks of Cancer Cells



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

Source: (84).

Health (NIH) budget has been allocated to basic research every year since 2003 (86).

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 5**, p. 32).

Collectively, knowledge gained from medical research has advanced cancer risk reduction, enabled innovative 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.

SIDEBAR 6

Commonly Used Models in Cancer Research

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 primary cells, tumors, or tissues that have acquired, either naturally or through manipulation, the ability to grow indefinitely.

PATIENT-DERIVED TISSUE FRAGMENTS are small pieces of a patient's tumor tissue obtained through biopsies or surgery. They retain the tumor's original structure and microenvironment, making them ideal for studying cancer behavior and drug response.

ORGANOIDS are engineered three-dimensional structures of cells generated from healthy or diseased tissues that can resemble an organ in cellular composition and organization.

PATIENT-DERIVED XENOGRAFTS, also called PDX models, are generated by transplanting pieces of a patient's tumor tissue into mice. A large number of therapeutics can then be tested for their ability to eliminate the patient's tumor in mice before they are given to the patient.

ANIMAL MODELS mimic normal or disease conditions. Mice are the most commonly used models, and numerous mouse models are used to study a variety of cancer types.

PRIMARY CELLS are obtained directly from healthy or cancerous tissues of either human or animal origin.

As detailed in the *AACR Cancer Disparities Progress Report 2024*, it is important to note that many of these research models lack ancestral diversity, and researchers are working to bridge this gap.

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 7**, p. 33). One notable example of this is the development of small molecule inhibitors of Kirsten rat sarcoma viral oncogene homologue (KRAS) protein, which is encoded by the *KRAS* gene, one of the most commonly mutated genes in human cancers. Mutations in the *KRAS* gene drive roughly 30 percent of all cancers, including some of the deadliest forms, such as pancreatic, lung, and colorectal cancers. For decades KRAS remained one of the most elusive targets in cancer because of the complex structure and function of the protein, often representing the prime example of an "undruggable" target.

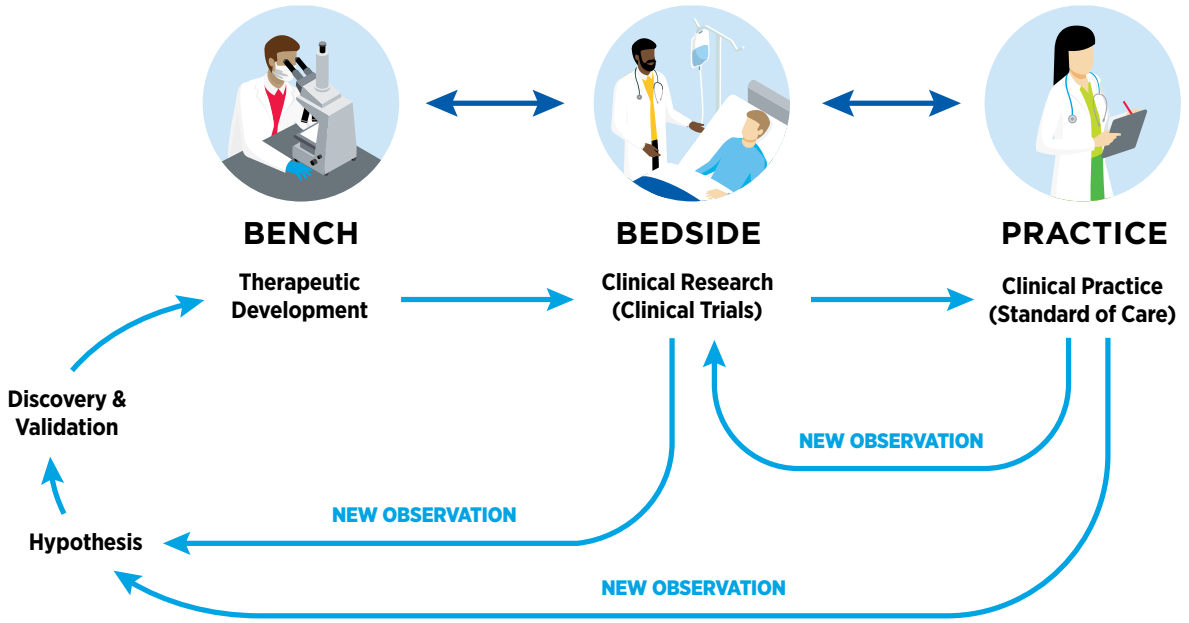
First discovered in 1982, the *KRAS* gene plays an important role in controlling how cells grow and survive. Researchers found that mutations in this gene can cause KRAS protein to be permanently turned "on," which can lead to uncontrolled cell growth and cancer development. Even though researchers understood early on through basic research discoveries that *KRAS* mutations could drive cancer, the protein's unique structure made it extremely difficult to target with drugs, since there were no obvious pockets for therapeutic molecules to bind.

Progress toward overcoming this challenge was eventually made possible through a series of fundamental research breakthroughs. Advances in understanding the three-dimensional (3D) shape of proteins uncovered a hidden "pocket" on a mutant form of KRAS, called KRAS G12C, and new chemistry tools helped researchers design drugs that could bind to it and inhibit its cancer-driving activity (87). These breakthroughs led to 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 36**, p. 109).

As of June 30, 2025, 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 5

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 the US Food and Drug Administration (FDA). Importantly, observations made during the routine use of a new therapeutic can further improve its use or inform the development of others like it. Even for therapeutics that are not approved by FDA, observations from preclinical and/or clinical testing can spur future research efforts.

In addition to 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.

For example, a recent study of sotorasib-treated patients identified factors both within tumor cells and the surrounding environment that render KRAS-targeted treatments less effective, which may lead to new strategies for overcoming resistance to KRAS inhibitors (88). In another study, researchers uncovered a previously unknown mechanism by which RAS proteins promote cancer progression, opening new opportunities to target previously unrecognized pathways (89).

All the while, basic and translational research continue to drive the development of next-generation KRAS-targeting drugs, including small molecule inhibitors that target mutations other than G12C or work more broadly against multiple forms of KRAS—known as pan-KRAS inhibitors—which could help treat cancers beyond colorectal and lung. In addition to inhibitors, researchers are also developing protein degraders, a class of therapeutics that can eliminate KRAS proteins from cancer cells and immunotherapies designed to recognize and attack KRAS-mutated cells (see **Sidebar 56**, p. 206).

Driven by the success of KRAS, researchers are now pursuing other challenging molecular targets, such as MYC and TP53, which are also commonly altered in many cancers. Decades of effort to inhibit MYC and TP53 are beginning to translate into tangible progress, with several compounds entering clinical

SIDEBAR 7

Basic Research Driving Clinical Advances Against Cancer

Basic Research Discoveries	Clinical Breakthroughs (As of June 30, 2025)
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, gastric, lung, biliary tract,** and **colorectal cancers**, as well as **any solid tumor with a specific HER2 biomarker**.
1980s The *PARP-1* gene is identified and its role in DNA repair is discovered. **1990s** The *BRCA1* and *BRCA2* genes are identified and their role in DNA repair is discovered.	Since FDA's 2014 approval of the first molecularly targeted therapeutic that inhibits PARP activity—olaparib (Lynparza)—to treat BRCA-mutated **advanced ovarian cancer**, at least one PARP-targeted therapeutic has been approved for the treatment of **breast, ovarian, pancreatic,** and **prostate cancers**.
1980s The *NTRK* gene is identified and its rearrangements in **colorectal** and **thyroid cancers** are documented.	Since FDA's 2018 approval of the first molecularly targeted therapeutic that inhibits NTRK activity—larotrectinib (Vitrakvi)—to treat children and adults whose **tumors are carrying *NTRK* rearrangements**, two additional NTRK-targeted therapies have now been approved by FDA for treatment of **any solid tumor based on *NTRK* rearrangements**.
1980s T-cell receptor is discovered and cloned.	The first T-cell receptor (TCR) T-cell therapy—afamitresgene autoleucel (Tecelra)—was approved by FDA in 2024 to treat **synovial sarcoma**.
1990s The *KMT2A* gene is identified and its chromosomal translocations are recognized as drivers of **acute leukemias**. **2000s** The pivotal role of menin, a protein encoded by the *MEN1* gene, in facilitating interactions with the KMT2A protein is discovered.	The first molecularly targeted therapeutic that inhibits menin activity—revumenib (Revuforj)—was approved by FDA in 2024 to treat **leukemias** in both adults and children with *KMT2A* translocations.
2000s The *IDH1* and *IDH2* genes are identified and their roles in **glioma** development are discovered.	Since FDA's 2017 and 2018 approvals of the first molecularly targeted therapies inhibiting IDH2 and IDH1—enasidenib (Idhifa) and ivosidenib (Tibsovo), respectively—for the treatment of *IDH*-mutant **leukemias**, four IDH-targeted therapies have now been approved. Notably, this includes FDA's 2024 approval of vorasidenib (Voranigo), the first dual IDH1/2 inhibitor and the first systemic targeted therapy approved specifically for **low-grade glioma** with *IDH* mutations.
2010s The role of *NRG1* gene fusions as a driver of **lung cancer** is discovered.	The first molecularly targeted therapeutic that inhibits NRG1 activity—zenocutuzumab (Bizengri)—was approved by FDA in 2024 to treat patients with **lung** or **pancreatic cancers** harboring an *NRG1* gene fusion.

trials and showing early signs of safety and efficacy (90). Moreover, researchers have shown that many drugs targeting specific genetic alterations—such as those in the *ALK*, *BRAF*, *NTRK*, and *RET* genes—are effective across multiple tumor types, including lung, thyroid, melanoma, and in certain pediatric and rare cancers. In some cases, these therapies have

enabled clinical trials and regulatory approvals for both adults and children simultaneously. As advances continue, the tools and insights gained from basic research are paving the way for innovative therapies aimed at tackling other difficult-to-treat cancers that have long resisted traditional approaches.

Cancer Development: Translating Knowledge to Understand the Biology of Cancer

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

As cancer progresses, cells accumulate additional changes that allow them to grow more aggressively, evade the immune system, and adapt to their environment. This continuous evolution leads to significant molecular and cellular differences among cells within a single tumor, a phenomenon known as tumor heterogeneity. 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. These differences can affect how tumors grow and respond to treatment. 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 treatment.

Influences Inside the Cell

Cells store their genetic instructions in a molecule called deoxyribonucleic acid (DNA). These instructions, encoded in DNA, guide the cell's growth, function, and multiplication. DNA consists of two strands made up of repeating units called nucleotides, comprising one of four chemical bases—adenine (A), thymine (T), cytosine (C), or guanine (G). The two DNA strands pair together to form a double helical structure. The entirety of a person's DNA is called the genome. In human cells, DNA resides within the cell's nucleus, where it is tightly wrapped around proteins called histones. This DNA–protein complex, known as chromatin, is further compacted into larger structures called chromosomes. Most human cells contain 46 chromosomes.

Each chromosome contains hundreds to thousands of genes, which are segments of DNA that contain specific instructions. The cell uses a complex process, called transcription, to copy the instructions from genes into molecules known as messenger ribonucleic acid (mRNA). These mRNA molecules are then used in a separate process called translation to make proteins that perform a wide range of essential functions in the body. The following sections explore the types of changes within the cell that can lead to cancer development.

Genetic Alterations

One of the hallmarks of cancer cells is alterations in the DNA sequence. Also called mutations, genetic alterations 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 (germline mutations) or acquired throughout a person's lifetime (somatic mutations) (see **Sidebar 8**, p. 35). Whether inherited or acquired, genetic mutations tend to disrupt normal cellular functions. For example, mutations can activate oncogenes (genes that promote cell growth) or inactivate tumor suppressor genes (genes that restrict cell growth), both of which can lead to uncontrolled cell proliferation.

Germline mutations play a critical role in determining the inherited risk of developing cancer. About 10 percent of cancer 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. Although not all germline mutations carried by a parent are passed down, those that are become incorporated into the DNA of every cell in the body of the offspring. These types of mutations can increase their risk of developing cancer; however, not all germline mutations contribute to cancer development. Genetic alterations not associated with an increased risk of cancer are referred to as benign variants, whereas those that contribute to cancer development are classified as pathogenic variants. However, even among pathogenic variants, some genetic alterations confer a higher risk of developing cancer than others (see **Figure 6**, p. 36).

Technological advances in DNA sequencing have enabled a better understanding of germline pathogenic mutations and their association with a person's risk of developing cancer. A recent study analyzing whole-genome sequences from nearly 865,000 individuals identified germline mutations in six genes not previously associated with inherited cancer risk. These mutations were linked to either increased or decreased risk of developing specific cancers, including prostate, colorectal, thyroid, lung, melanoma, and breast cancers (91). These findings provide new insights into how inherited mutations contribute to cancer susceptibility and may offer new opportunities to inform early detection strategies and therapeutic interventions.

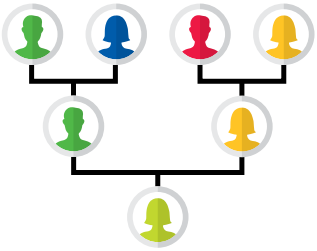
SIDEBAR 8

What Are Genetic Alterations?

Genetic alterations include changes in the DNA sequence. While not all genetic alterations cause cancer, many result in changes in the sequence or amount of messenger ribonucleic acid (mRNA) and/or proteins produced that can drive or contribute to cancer development. Genetic alterations are a hallmark of cancer cells.

How Do Genetic Alterations Arise?

BY INHERITANCE FROM PARENTS (GERMLINE MUTATIONS)



ACQUIRED DURING A PERSON'S LIFETIME FROM (SOMATIC MUTATIONS)

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

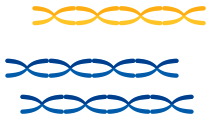
What Types of Genetic Alterations Contribute to Cancer Development?

SINGLE BASE CHANGE

Refers to deletion, insertion, or substitution of a single nucleotide—or "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.

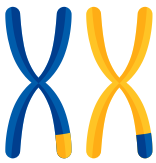
GENE AMPLIFICATION

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



STRUCTURAL GENETIC 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.



DELETION

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

In addition to large-scale sequencing efforts that identify potential risk-associated inherited genetic variants, emerging genome editing technologies are now making it possible to directly test the biological impact of these mutations. CRISPR-based systems are powerful and versatile gene editing tools that allows researchers to precisely modify DNA (see **CRISPR in Cancer Research and Drug Development**, p. 201). In two recent studies, researchers used large-scale CRISPR-based screening to test nearly all possible single base changes in the *BRCA2* gene, which is often linked to inherited risk in breast and ovarian cancers. This approach allowed them to assess the functional impact of thousands of previously unclear genetic changes, known as variants of unknown significance, and determine whether they were benign or pathogenic (92,93).

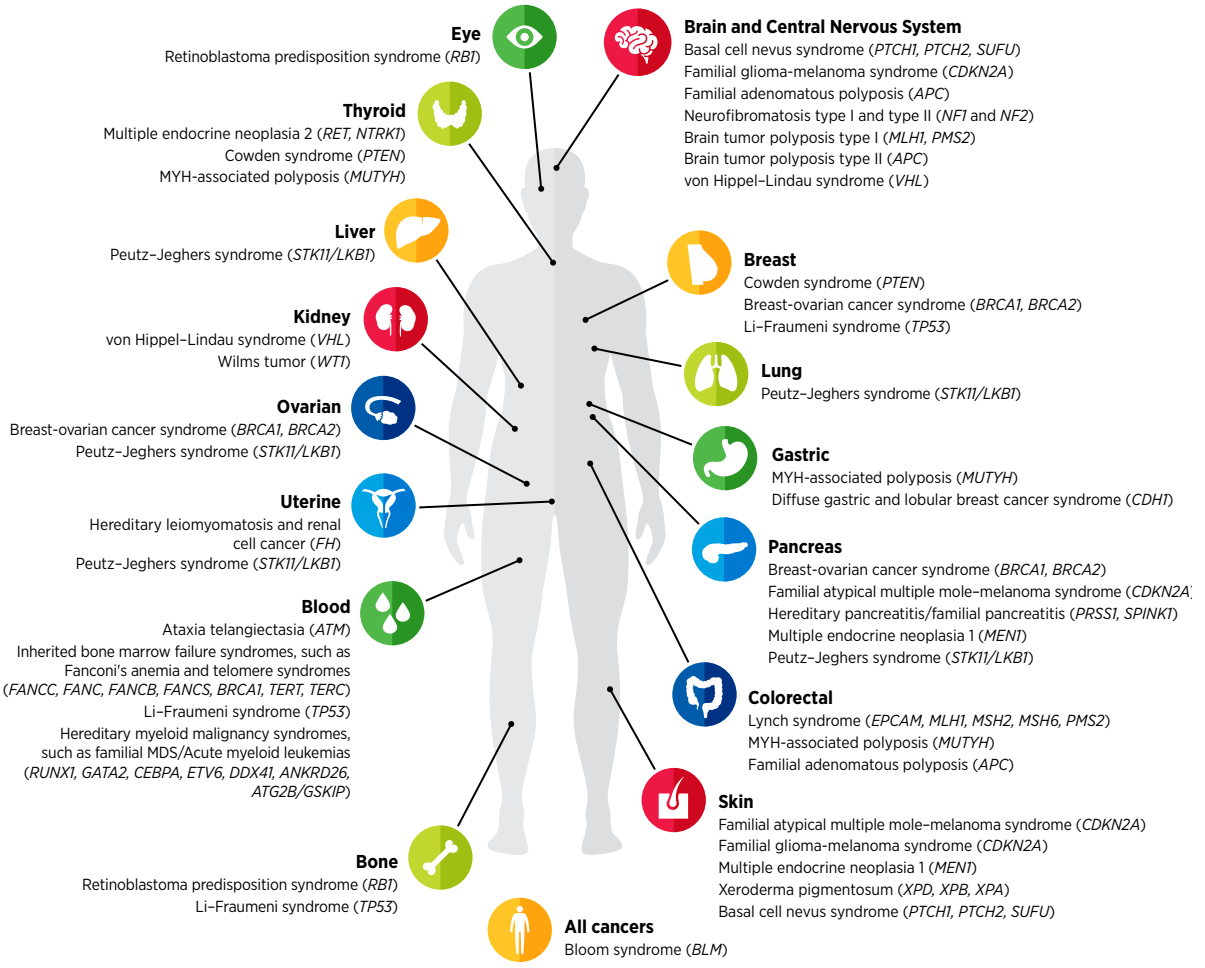
Findings from these studies provide a powerful resource for better understanding *BRCA2* inherited mutations and enhancing clinical management for individuals who carry them.

Somatic, or acquired, mutations arise during an individual's lifetime, often because of 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 mutation patterns reflecting their potential causes, tissue of origin, and evolution over time.

Recent research has emphasized the importance of understanding how somatic mutation patterns can vary by

FIGURE 6

Inherited Cancer Risk



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

age, as these differences may influence cancer development, progression, and response to treatment. A study examining early-onset colorectal cancer revealed that tumors diagnosed in younger adults often carry a different set of genetic alterations than those found in older patients (see **The Growing Population Burden of Cancer**, p. 23, and **Sidebar 4**, p. 25). Some of these mutations may affect how tumors grow, while others are linked to how well patients respond to certain therapies (94). The study also found that these molecular features can differ by ancestry, highlighting the need for inclusive research to better understand cancer in all populations. Similarly, a recent study of breast cancer found that tumors in older adults often carry different genetic changes than those in younger patients. These age-related differences may affect how tumors behave and respond to treatment, especially in metastatic disease (95). Together, these studies suggest that age plays a critical role in shaping cancer biology, emphasizing the need for age-tailored approaches to diagnosis and treatment across cancer types.

In addition to advances in understanding how genetic mutations drive cancer development, researchers are increasingly exploring nontraditional DNA structures that have historically been understudied. In recent years, extrachromosomal DNA (ecDNA)—circular DNA fragments that exist outside chromosomes—has emerged as a key contributor to tumor growth, treatment resistance (see

Sidebar 37, p. 110), and poor clinical outcomes across cancer types (see **Sidebar 9**, p. 37). 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 ecDNAs are present in approximately 17 percent of human cancers and are often associated with the overproduction of oncogenes, greater genetic heterogeneity within tumors, the ability of cancer cells to evade the immune system, and resistance to therapy (96–98).

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 Fueling Precision Medicine**, p. 46). Just in the past year, notable progress has been made in ecDNA detection and our understanding of how it drives cancer (99,100). Researchers have recently developed an innovative animal model that allows ecDNA-driven cancer to be studied in real time, providing a powerful tool to uncover how these unique DNA elements contribute to tumor progression (101). New research has shown that ecDNA can lead to conflicts between the cell's DNA copying and RNA producing machineries. This disruption creates unique vulnerabilities in a cancer cell that may be targeted with therapies, such as CHK1 inhibitors, which block a protein that helps cells repair DNA damage. A first-in-human clinical trial is now underway to evaluate CHK1 inhibitors in cancers driven by ecDNA (102). Together, these discoveries establish ecDNA as a critical driver of cancer and an exciting new area for therapeutic development.

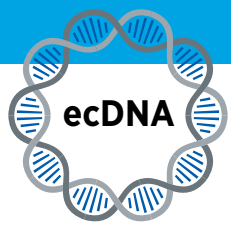
Researchers are building on the understanding of genetic alterations that drive cancer development to inform new strategies for cancer prevention, diagnosis, and treatment. Over the past two decades, FDA has approved numerous targeted therapies designed to inhibit the effects of specific genetic mutations found in cancer cells (103). 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 **Genetic Insights Advancing Cancer Risk Reduction and Interception**, p. 85).

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, depending on the cell's needs. This regulation allows cells to

SIDEBAR 9

Extrachromosomal DNA in Cancer



Extrachromosomal DNA (ecDNA)—circular DNA fragments that exist outside chromosomes—has recently been identified as a key contributor to cancer development, progression, and treatment resistance. These fragments frequently contain oncogenes that can be rapidly amplified to drive aggressive tumors.

Why Does ecDNA Matter in Cancer?

HIGH ONCOGENE EXPRESSION

ecDNA often harbors multiple copies of oncogenes, leading to abnormally high expression that fuels uncontrolled cell growth.

GENOME INSTABILITY

ecDNA formation and reintegration can reshape DNA structure, leading to genetic instability that promotes cancer progression.

TUMOR HETEROGENEITY AND EVOLUTION

ecDNA is unevenly distributed during cell division, increasing tumor heterogeneity and enabling resistance to therapies.

IMMUNE EVASION

ecDNA can reshape the tumor environment, helping cancer cells escape detection and destruction by the immune system.

TREATMENT RESISTANCE

ecDNA is not fixed in chromosomes, allowing it to rapidly increase copies of genes targeted by drugs, enabling them to adapt and become resistant to treatment.

ecDNA has been detected across many cancer types—including glioblastoma, lung, and colorectal cancers—and may serve as both a marker of poor prognosis and a window into new avenues for diagnosis and treatment. Tumors that contain ecDNA are often more aggressive and less responsive to conventional therapies. As research advances, targeting ecDNA may provide novel strategies against cancer progression and treatment resistance.

Source: (98).

fine-tune protein production as needed to respond to internal and external signals. In cancer, these regulatory processes often go awry. Cancer cells can increase the mRNA production for genes that promote survival and metastasis, while decreasing those that suppress growth.

Most human genes are made up of alternating 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, the introns are removed and the 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.

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.

If errors occur during the RNA splicing process, faulty mRNAs can produce dysfunctional proteins. In a recent study, aberrant splicing was found to play a critical role in driving tumor heterogeneity, proliferation, invasion, and therapeutic resistance in gliomas (104). Researchers are exploring the potential of targeting splicing mechanisms as innovative therapeutic strategies to restore normal splicing patterns or selectively eliminate aberrant splice variants that are associated with cancer (105).

Understanding how tumors change at the RNA level provides vital insights into how cancer develops, evolves, and spreads. Technologies such as transcriptomics and single-cell RNA sequencing are more often 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 10**, p. 39).

In a recent study, researchers conducted a large-scale transcriptomic analysis across multiple cancer types to understand how tumors adapt as they metastasize to new tissues. They found that while primary tumors largely resemble their tissue of origin, metastatic tumors exhibit gene expression profiles that resemble the tissues they spread to, particularly in metabolic and immune pathways (106). In addition, the study suggests that certain pathways in primary tumors already show gene expression patterns more similar to the metastatic target tissues than to the tissue of origin, highlighting transcriptomic changes that may drive or support metastasis.

In glioblastoma multiforme (GBM), a highly aggressive brain cancer, researchers used single-cell RNA sequencing to track tumor development from its earliest stages and uncovered a unique population of tumor cells with a neural crest–like identity, normally seen during early development or injury repair (107). These findings suggest that GBM may co-opt the brain's natural healing response to fuel tumor initiation.

Protein Modifications

The full set of proteins expressed by the cell, known as the proteome, contains approximately 20,000 unique proteins. Proteomics is the large-scale study of proteins, and research into the proteome of cancer cells has revealed important information about cancer that may not have been apparent from genomic or transcriptomic analyses alone. For example, using large-scale proteomic profiling, researchers recently identified three clinically distinct molecular subtypes of prostate cancer and developed a 16-protein panel that predicts recurrence more accurately than existing clinical methods. The study also found that two proteins from the panel play functional roles in promoting tumor aggressiveness, providing new potential molecular targets for prostate cancer therapy (108).

Proteogenomic research, which integrates proteomics, genomics, and transcriptomics, provides a comprehensive view of protein-level changes driving cancer that may be missed by DNA or RNA analysis alone (see **Sidebar 10**, p. 39). By analyzing proteogenomic data from over 1,000 patients across 10 cancer types, researchers identified proteins that cancer cells rely on to survive and grow. While some of these proteins are already targetable by available cancer drugs, others represent new opportunities for drug development or repurposing (109). These findings underscore the promise of proteogenomics in advancing precision medicine and guiding the development of more effective, targeted therapies.

The functions of many proteins are regulated by posttranslational modifications (PTMs), which are reversible chemical changes that modulate protein function, localization, and stability. In a recent study of more than 1,000 cancer patients across multiple tumor types, researchers introduced a precision proteogenomic approach to show that inherited genetic variants can change PTMs and protein stability, helping to explain differences between tumors that are not captured by gene expression alone (110).

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. Impaired protein degradation can contribute to cancer progression. A recent study showed that chaperone-mediated autophagy

SIDEBAR 10

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 cancer.

Types of Technologies*

TECHNOLOGY	IMPACT ON CANCER RESEARCH	UNIQUE STRENGTH
Whole-genome sequencing: Maps the entire sequence of a cell's genome.	Reveals both common and rare mutations that can contribute to cancer development.	Offers a comprehensive view of alterations across the entire genome, including previously unknown alterations.
Single-cell RNA sequencing: Measures gene expression in individual cells.	Captures gene expression differences between individual cells within a tumor and reveals tumor heterogeneity.	Detects cell-specific signals that would be lost in bulk cell population analysis.
Spatial omics (e.g., spatial transcriptomics, spatial proteomics): Maps molecular information, such as gene expression or protein distribution, across regions of intact tissues.	Shows how cancer cells interact with their environment in specific tumor regions.	Preserves spatial context to identify region-specific interactions and microenvironments.
Computational modeling tools: Uses algorithms and simulations to analyze biological data.	Predicts tumor evolution, treatment response, and identifies new therapeutic strategies.	Synthesizes complex data into testable hypotheses and clinical predictions.
Open-access platforms and big data portals: Provides access to public databases sharing cancer data.	Facilitates collaboration and accelerates discovery by making large datasets available to researchers.	Promotes transparency and democratizes data access to foster innovation and collaborative research progress.

Types of Biological Data*

GENOMICS

Data on the complete set of DNA in a cell that can be used to identify mutations and genomic drivers of cancer.

TRANSCRIPTOMICS

Data on all RNA molecules in a cell, showing which genes are turned on or off and used to measure gene expression and identify which genes are active in cancer cells.

PROTEOMICS

Data on all proteins in a cell, including their quantities, structures, and interactions, that can be used to identify disease markers and therapeutic targets in cancer.

EPIGENOMICS

Data on epigenetic changes in a cell, such as DNA methylation and histone modification, that reveal how gene regulation is altered in cancer.

METABOLOMICS

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

IMMUNOMICS

Data on the immune system, including the types of immune cells and the signals they use to communicate, that can help show how the body's defenses respond to cancer or are affected by it.

MULTI-OMICS

Data that integrate multiple layers of biological information—for example, proteogenomics combines genomic, transcriptomic, and proteomic data to link DNA and RNA alterations to protein expression—to provide a comprehensive view of the molecular changes underpinning cancer biology.

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

(CMA), a process that breaks down specific cellular proteins, helps suppress tumor spread by degrading proteins that promote metastasis. Researchers found that loss of CMA promotes epithelial-to-mesenchymal transition, a process by which cancer cells become more flexible and able to move, which in turn drives more aggressive tumor growth (111). These findings demonstrate a mechanistic link between impaired protein degradation and metastatic progression, revealing the therapeutic potential of processes that cause controlled protein degradation in cancer.

In individuals under the age of 50, each year of **epigenetic age acceleration is associated with a 16% increase in the odds of having precancerous colon polyps**, suggesting a potential role for biological age in guiding early colorectal cancer screening.

Source: (118).

W11

Epigenetic Changes

Epigenetic modifications are chemical changes that regulate gene activity without altering the underlying DNA sequence. The entirety of epigenetic changes within a cell is called the epigenome. These changes involve the addition or removal of chemical marks on DNA and modifications to histones, the proteins that package DNA into chromosomes. Epigenetic alterations can be shaped by aging, environmental exposures, lifestyle factors, and chronic stress. In healthy cells, these mechanisms tightly regulate gene expression, but in cancer, this regulation is disrupted.

Epigenetic changes are now being linked with different aspects of cancer development. For example, researchers have identified that brain metastases rely on epigenetic alterations, which lead to changes in gene activity by turning genes on or off, enabling cancer cells to survive and thrive in the brain's unique microenvironment (112).

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 active or silenced. In a recent study, researchers developed a DNA methylation–based model using tumor and plasma samples from patients with lung cancer to accurately predict the risk of brain metastases (113). This study highlights the clinical potential of DNA methylation profiles as noninvasive biomarkers—measurable molecular markers that can indicate disease presence, risk, or treatment response—for identifying patients at risk for brain metastases, supporting earlier intervention and more personalized care.

Epigenetics also plays a central role in how tumors evolve and resist treatment. In a recent study, researchers used Hi-C, a high-throughput genomic and epigenomic technology that captures the spatial organization of chromatin in a cell, to examine tumor and nearby normal brain tissue from nine patients with GBM. By mapping the 3D organization of DNA, they found that changes in the genome's structure can disrupt normal gene regulation by altering which DNA regions interact. These changes can switch genes on or off inappropriately, potentially driving tumor growth (114). These findings reveal that the epigenetic landscape of GBM is shaped by the tumor genome's 3D structure and point to new therapeutic vulnerabilities that could be targeted to disrupt these altered regulatory patterns.

Epigenetic regulation is also influenced by aging and the immune system. 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 actual chronological age—known as epigenetic age acceleration—it may signal increased cancer risk. A recent study found that aging of the immune system leads to epigenetic changes that weaken the body's ability to fight cancer, allowing immunosuppressive cells to build up and support tumor growth (115). In contrast, another study showed that aging may help protect lungs from developing cancer by weakening the ability of certain lung cells to become cancerous. This protective effect was linked to aging-associated epigenetic changes that lead to the loss of cancer-promoting features of lung cells (116). Together, these findings highlight the complex role of epigenetic regulation in cancer, showing that aging-related changes can either suppress tumor initiation or promote tumor growth, depending on the cellular context. This may help explain why, although cancer risk generally increases with age, incidence declines slightly among the oldest individuals (117).

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.

Influences Outside the Cell

In addition to alterations inside the cell, influences outside the cell contribute to cancer development, progression, and response to therapy (see **Sidebar 11**, p. 41). These external factors include systemic influences, such as hormones and nutrients in the circulation, as well as local tissue environments that interact

SIDEBAR 11

Cancer Growth: Local and Systemic Influences

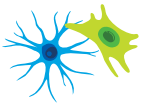
Solid tumors are much more complex than an isolated mass of dividing cancer cells. Cancer development is strongly influenced by interactions between cancer cells and numerous factors in their environment.

Among the components of the tumor microenvironment are:

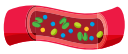
IMMUNE CELLS that can identify and eliminate cancer cells, although in many cases cancer cells acquire characteristics that help them evade the immune system, permitting the formation and progression of a tumor.

A NETWORK OF BLOOD AND LYMPHATIC VESSELS in and around the tumor that is stimulated by cancer cells through a process called tumor angiogenesis supports rapid growth and survival of cancer cells through increased supply of nutrients and oxygen and provides an escape route to distant sites (metastasis).

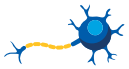
A MATRIX OF PROTEINS that surrounds tumor cells and provides structural and biochemical support. Formed partly in response to chemical signals from cancer cells, this matrix regulates the proliferation of cancer cells, supports tumor growth, and can aid in tumor metastasis.



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



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.

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 (84). This process—known as metastasis—is enabled by circulatory systems, such as the blood and lymphatics, which can 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 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.

Circulatory and Immune Systems

The circulatory and immune systems—including the blood, lymphatic, and immune networks—play essential and interconnected roles in cancer initiation, progression, and response to treatment. These systems influence how tumors grow, spread, and interact with their surrounding environment, shaping both disease course and therapeutic outcomes.

The blood system, composed of blood vessels and the cells and signals that circulate within them, is essential for delivering oxygen and nutrients throughout the body. It also supports immune surveillance, the process by which the immune system constantly monitors the body for the presence of abnormal or damaged cells, including cancer cells. Angiogenesis is the formation of new blood vessels, a process that occurs naturally throughout a person's life. Multiple chemical signals in the body control this essential process. Cancer cells acquire the ability to promote angiogenesis toward and within a tumor to meet the high demand of oxygen and nutrients needed to fuel rapid tumor growth.

Decades of research have revealed multiple proteins and chemicals that regulate normal blood vessel formation, many of which are hijacked by cancer cells to promote tumor angiogenesis. For example, the protein vascular endothelial growth factor (VEGF) and its cell surface binding partner, called the VEGF receptor, are necessary for angiogenesis and play a crucial role in the growth of cells that line the inside of blood vessels. Cancer cells can produce and release high levels of VEGF, thus directing the formation of new blood vessels in and around tumors. VEGF can also limit the function of certain cancer immunotherapies known as chimeric antigen receptor (CAR) T cells (see **Sidebar 41**, p. 135). In a recent study, researchers engineered CAR T cells to secrete a VEGF-blocking molecule directly within tumors, enhancing both their antitumor activity and their ability to infiltrate solid tumors (119).

Over the past two decades, several drugs that block angiogenesis have been approved to treat cancer. More recently, advances in our understanding of the cellular and molecular mechanisms driving angiogenesis are informing the development of novel therapeutic strategies. In one recent study, researchers showed that low doses of certain chemotherapeutic agents can inadvertently enhance tumor growth and metastasis in mouse models (see **Sidebar 6**, p. 31). This effect was driven by increased angiogenesis and immune suppression through increased circulation of proangiogenic and immunosuppressive bone marrow–derived cells, underscoring the importance of optimal dosing strategies to avoid unintended pro-tumorigenic effects (120). Researchers have also shown that combining antiangiogenic agents with cancer immunotherapies known as immune checkpoint inhibitors (ICIs) could further improve immunotherapy outcomes, offering therapeutic opportunities for more precisely disrupting tumor blood supply and enhancing treatment efficacy (121).

The lymphatic system is an extensive network of vessels—known as lymphatic or lymph vessels—along with lymph nodes and several organs including the spleen, thymus, tonsils, and adenoids. It plays an important role in maintaining total fluid balance, removing cellular waste from tissues, detecting pathogens, and producing immune cells and antibodies within lymph nodes.

One way that cancer cells travel to other parts of the body is through the lymphatic system. 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.

Tumors can also stimulate the formation of new lymphatic vessels—a process known as lymphangiogenesis—by releasing proteins, such as a form of the VEGF protein called VEGF-C. These proteins promote lymphatic vessel remodeling and increase opportunities for cancer cells to access and spread through the lymphatic system, particularly to nearby lymph nodes.

Researchers have found that while tumor-associated lymphangiogenesis is often linked to cancer progression, it may also help the immune system fight cancer. In melanoma and colorectal cancer, more lymphatic vessels in primary tumors were found to correlate with more inflammation and increased immune cell activity in the tumor. Furthermore, VEGF-C expression in metastatic melanoma was associated with better outcomes following treatments with immunotherapeutics (122). These findings suggest that changes to the structure and function of lymphatic vessels in tumors may promote immune activation and improve response to immunotherapy.

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 they work together to detect and remove pathogens, as well as abnormal or damaged cells from the body. The immune system has two main components. The innate immune system is the body's first line of defense that provides a general, nonspecific response to pathogens. It includes physical barriers, such as the skin and mucous membranes, as well as certain immune cells and molecules that quickly 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 39**, p. 129).

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 brakes on the system to suppress T-cell responses and recruiting immunosuppressive cells. Another way cancer cells escape immune detection involves the release of proteins that impair immune cell function. In a recent study, researchers showed that melanoma cells can secrete a protein that disrupts dendritic cell function and impairs T-cell activation, thus promoting immune resistance and disease progression (123).

In other cases, cancer cells can disrupt cellular machinery used by immune cells to recognize damaged or abnormal cells. For example, a recent study revealed that breast cancer cells can reprogram surrounding immune cells through metabolic cross-talk, manipulating the nutrients available in their environment to transform immune cells that would normally fight cancer into ones that help it grow. This reprogramming suppresses T cell response and reshapes the tumor microenvironment (124). Identifying immune evasion strategies can reveal new targets for therapeutic development and improve the effectiveness of immune-based cancer therapies.

A recent study demonstrated that the dynamic relationship between cancer and the immune system can be shaped by a person's inherited mutations, which influence how well the immune system recognizes proteins derived from certain cancer-driving genes. For example, researchers found that individuals whose immune systems could more effectively recognize HER2 protein were less likely to develop HER2-positive breast cancer. These findings suggest that inherited genetic factors can shape how the immune system detects and responds to cancer, thereby influencing both cancer risk and tumor evolution (125).

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 40**, p. 130). In a recent study, researchers discovered that a protein called ID3 helps maintain a pool of specialized T cells that can sustain immune responses against cancer over time. Boosting ID3 activity improved tumor control in preclinical models, highlighting its promise as a way to strengthen response to immunotherapies (126). 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.

The Nervous System

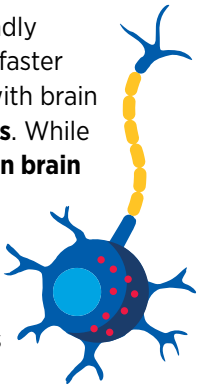
The nervous system is becoming more recognized as a key regulator of cancer development. Research has uncovered dynamic interactions between the nervous system and cancer as drivers of tumor growth, metastasis, immune evasion, and resistance to therapy, giving rise to the emerging interdisciplinary field of cancer neuroscience. In recognition of the complexity and clinical importance of this topic, the Cancer Grand Challenges initiative recently launched a new challenge to catalyze research efforts aimed at unraveling interactions between the nervous system and cancer (see **Technological Innovations Fueling Precision Medicine**, p. 46).

The nervous system—composed of the central nervous system (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. Interactions between the nervous system, the immune system, and cancer take place both within the local tumor microenvironment and systemically throughout the body.

Nerve cells, or neurons, interact with cancer cells by releasing signaling molecules and transmitting electrical signals through direct contact, which influence nearby immune and stromal cells—the supportive cells that make up certain types of connective tissue—within the tumor microenvironment. Using an innovative single-cell transcriptomic technology (see **Sidebar 10**, p. 39), researchers recently identified distinct subtypes of peripheral neurons that infiltrate pancreatic tumors, and investigated how these neurons interact with other cells in the tumor microenvironment. They found that pancreatic cancer cells reprogram these neurons, creating a network of interactions between nerve cells, cancer cells, and the surrounding microenvironment that influences tumor growth, immune infiltration, and therapy response. Blocking nerve signals using therapeutics created a more immune-friendly environment and enhanced the effectiveness of ICIs, opening a new avenue for cancer treatment (127).

In another study, researchers discovered a direct connection between nerve cells and gastric cancer cells that was mediated by CGRP—a chemical released by nerve cells that promotes tumor growth, metastasis, and immunosuppression. Inhibiting CGRP signaling with a migraine drug, rimegepant

Diffuse midline gliomas—a deadly childhood brain cancer—grow faster when they form connections with brain cells called **GABAergic neurons**. While **these cells normally slow down brain activity, they may also drive tumor growth.** Tumor growth is further accelerated when patients are given lorazepam, a common sedative that works by enhancing GABA signaling.



Source: (129).

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(Nurtec ODT), significantly reduced tumor burden and prolonged survival in preclinical models (128). These findings highlight cancer–nerve interactions as promising targets for therapeutic intervention.

Other cancer cells appear to acquire neuron-like features themselves. Recent research revealed that neuroendocrine cells—cells that release hormones into the blood in response to stimulation by the nervous system—in small cell lung cancer can produce electrical signals that directly promote tumor progression and aggressiveness. Even cells that do not produce electrical signals support this activity by supplying nutrients to cancer cells, which help fuel the high energy demands of electrical signaling (130). These findings highlight new insights into tumor growth driven by electrical activity.

Scientists are uncovering 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 human 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. 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. Studies have shown that microbiomes throughout the body play essential roles in digestion, metabolism, immune system regulation, and protection against pathogens. A growing body of research suggests that these microbial communities may also influence cancer development and treatment response by shaping immune activity, inflammation, and the tumor microenvironment (84).

A recent study highlighted how changes in the composition of the gut microbiome contribute to the initiation and progression of colorectal, gastric, liver, and pancreatic cancers. Beyond its role in cancer development, the microbiome can also shape responses to treatment by enhancing drug metabolism, reducing toxicity and side effects, and promoting antitumor immunity (131). For example, a recent study found that using low doses of radiation to the gut improved the effectiveness of PD-L1 immunotherapy in patients with metastatic cancer, but this response was strongly influenced by the composition of each patient's gut microbiome (132).

An analysis of 175 patients with melanoma revealed that low gut microbial diversity was associated with poor response to immunotherapy (133). Higher abundance of specific gut-associated bacteria was linked to better outcomes, including

Regular yogurt intake was linked to a **lower risk of certain colorectal cancers**, particularly yogurts with detectable levels of *Bifidobacterium*, a common probiotic.

Source: (134).

W13

survival without signs of cancer progression for at least 12 months and a more active immune response against cancer. In contrast, the use of broad-spectrum antibiotics, which can reduce microbial diversity and eliminate beneficial bacteria, was associated with poorer outcomes from immune checkpoint blockade. These findings suggest that the gut microbiome may influence how well cancer therapies work, and larger studies are needed to further establish the role of modulating the microbiome through lifestyle and therapeutic interventions, such as dietary changes or probiotic use, to improve cancer treatment outcomes.

Efforts to understand the impact of the gut microbiome on cancer have led to large-scale international collaborations, such as the ONCOBIOME network, to investigate the gut microbiome's role in cancer development and treatment response, with the goal of using the microbiome to develop effective ways of diagnosing and treating cancer. Analyzing over 12,000 fecal samples from over 9,800 patients with cancer and healthy donors, researchers characterized how microbial communities influence the immune system and therapeutic outcomes. The ONCOBIOME initiative also developed diagnostic tools that helped identify microbes with the ability to activate or suppress immune response, laying the groundwork for personalized microbiome-based therapeutic interventions (135).

Beyond the gut, researchers recently showed that breast tissue has a distinct modifiable microbiome population. They found that tamoxifen, a common hormone therapy for breast cancer, alters the breast tissue microbiome, particularly by increasing beneficial bacteria, such as *Lactobacillus spp*. This increase in beneficial microbes can suppress tumor growth and reduce proliferation in estrogen receptor–positive breast cancer models (136). These findings suggest that the breast microbiome actively influences tumor metabolism and progression, and that targeting it may enhance breast cancer prevention and treatment strategies.

Emerging research has also shown that the oral microbiome may play a direct role in the development of pancreatic cancer, one of the most lethal cancer types. Certain oral bacteria have been identified within pancreatic tumors and may promote cancer progression by inducing chronic inflammation and disrupting immune function (137). However, more research is needed to further characterize the microbiome inside tumors and determine their influence on cancer development.

The fungal microbiome, or mycobiome, is emerging as another contributor to cancer initiation, progression, and treatment outcomes. Researchers are exploring how fungi influence the tumor microenvironment, and whether this knowledge can be used to develop effective treatments for cancer (138). For example, a recent study identified different types of fungi, such as *Candida* and *Malassezia*, across various cancer types, where they promote inflammation and immune suppression (139). As technologies for fungal detection and analysis improve, it will be important to evaluate whether the mycobiome can be leveraged to diagnose and treat cancer.

It is becoming increasingly clear that targeting the microbiome may help improve health outcomes for patients with cancer. 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. In parallel, microbiome profiling may also become an integral component of predicting how patients may respond to cancer treatment, particularly immunotherapy.

Tumor Microenvironment

The tumor microenvironment (TME)—composed of cancer and non-cancer cells, blood vessels, signaling molecules, and structural components—is a dynamic ecosystem 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 11**, p. 41). The full collection of proteins and molecules released by cells into their surroundings is known as the secretome. Tumor cells often alter the composition of their secretome, affecting the behavior of nearby healthy cells and influencing distant tissues to support tumor progression.

Understanding the TME is essential for 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 10**, p. 39) 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 tumor growth, metastasis, and resistance to therapy. In a recent study, researchers used single-cell and spatial transcriptomics to uncover treatment-induced remodeling of the TME in pancreatic cancer and found that elevated signaling of IL-6, which helps cancer cells communicate with their surroundings, promotes resistance to cancer treatment through enhanced cell survival and epithelial-to-mesenchymal transition (141).

Emerging evidence suggests that **fibroblasts and innate immune cells drive chronic inflammatory responses**. This response reshapes the tumor microenvironment by promoting immunosuppression, matrix remodeling, and cancer cell invasion, driving tumor progression and therapy resistance.

Source: (140).

W14

Studying the TME in cancers that metastasize to the brain may offer valuable insights into why these tumors are often difficult to treat and resistant to standard therapies. To better understand this environment, researchers are using advanced single-cell and spatial tools that analyze individual cells and their activity within the tumor's structure. In two recent studies, researchers built detailed maps of brain metastases across several cancer types, revealing features that help tumors survive in the brain microenvironment (142,143). 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.

Within the TME, the tumor immune microenvironment (TIME) specifically refers to the network of immune cells and immune-modulating factors that interact with the tumor. The TIME plays an important role in cancer progression, and a deeper understanding of the processes within this environment is essential for developing 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. These changes are driven by several interconnected biological processes, including cellular senescence—a state in

A recent study showed that **aspirin disrupts a key mechanism that suppresses the immune system**, thereby enhancing T cell activity and reducing cancer metastasis.

Source: (145).

W15

which cells permanently stop dividing in response to stress, damage, or aging signals but remain metabolically active—and chronic inflammation. 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 (144). Therapies that target senescent cells, reduce inflammation, or enhance immune activity may reshape the aging TIME and improve clinical outcomes.

Cancer Development: Integrating Knowledge to Advance 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 12**, p. 46). 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 treating patients based on characteristics that distinguish them from other individuals with the same disease (see **Figure 7**, p. 47). 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 Fueling Precision Medicine

By leveraging emerging technologies and multi-omic data (see **Sidebar 10**, p. 39), 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.

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 proving 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 6**, p. 31) (146). Harnessing the strengths of both TCGA and DepMap, researchers have recently developed an

SIDEBAR 12

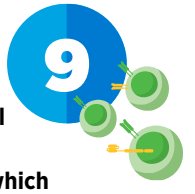
The Therapeutic Impact of Understanding Cancer Biology

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 FDA-approved therapeutics that target specific molecules involved in cancer**.

Advances in understanding that cancers arising in different tissues can be driven by the same genetic alterations has led to **9 FDA-approved site-agnostic therapies—such as those targeting *NTRK* gene fusions—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**.

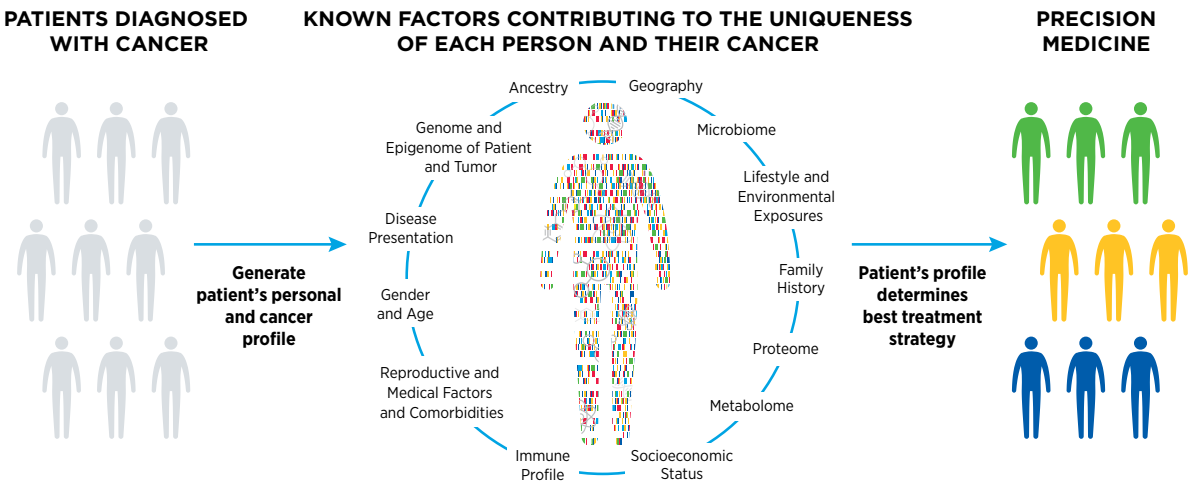
Knowledge that cancer cells evade immune destruction by exploiting immune checkpoint pathways has led to the development of **15 FDA-approved inhibitors targeting PD-1, PD-L1, CTLA-4, and LAG-3 immune checkpoints**.



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**.

FIGURE 7

Precision Medicine



Precision medicine, also called personalized medicine, is broadly defined as treating patients based on characteristics that distinguish them from other individuals with the same disease. As shown in the figure, the factors that contribute to the uniqueness of a patient and 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, gender, ancestry, environmental exposures, lifestyle, and comorbidities.

Currently, genomics is the predominant factor influencing precision medicine, but as we learn more about the additional factors, such as epigenomics, tumor immune characteristics, microbiome, and so on, we have begun to integrate this knowledge to further refine the personalized approach to cancer treatment. Although genomic profiling of a patient and of the patient's tumor is becoming routine in the clinic, it is important to note that there are stark disparities in the utilization of these services, with lower uptake among medically underserved populations.

artificial intelligence (AI) tool that identifies critical genes or pathways that tumors depend on to grow and survive (see **New Advances in Artificial Intelligence**, p. 194, and see **Sidebar 54**, p. 198) (147).

These initiatives have also transformed our understanding of cancer biology by promoting structured, large-scale collaboration across institutions. While the value of collaborative frameworks was established by efforts like the Human Genome Project and TCGA, researchers have recently proposed a framework that builds on this by defining specific "Hallmarks of Cancer Collaboration" to help modern cancer teams align incentives, share resources, and pursue common goals. This framework emphasizes the need for deliberate, coordinated efforts to translate big data into meaningful clinical advances (148).

The Human Tumor Atlas Network (HTAN) is another example of a next-generation, collaborative, data-intensive cancer research initiative. HTAN projects apply advanced technologies that examine individual cells and their molecular features within the structure of tumors through single-cell and spatial multi-omic technologies—including transcriptomics, proteomics, epigenomics, and advanced imaging—to map the cellular and molecular architecture of tumors throughout the course of disease progression and treatment (149–151). The comprehensive tumor maps, or atlases, are helping researchers understand how distinct cell types and cellular states arise during tumor evolution and the emergence and expansion of therapy-resistant cell populations (151–153).

HTAN studies also reveal how the TME adapts in response to therapy, including changes in immune cell infiltration, fibroblast activity, and extracellular matrix remodeling (154,155). In parallel, HTAN studies are uncovering how the ability of cancer cells to change their identity—such as by mimicking developmental programs or reverting to a less specialized state—and switching between cell types contribute to therapy resistance and tumor recurrence (156,157). By capturing the complexity of tumors over time and space, HTAN is informing efforts to design treatment strategies that can be modified based on tumor stage, molecular characteristics, and response to therapy (see **Sidebar 13**, p. 48) (158,159).

SIDEBAR 13

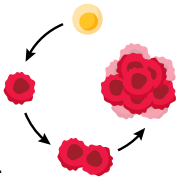
The Human Tumor Atlas Network

Launched as part of the Cancer Moonshot, the Human Tumor Atlas Network (HTAN) is a collaborative research initiative that aims to create dynamic, multidimensional maps—or "atlases"—of human tumors as they evolve from precancerous lesions to malignant disease and in response to treatment. By integrating cutting-edge technologies and open-access data sharing, HTAN is revealing how cancer transforms over time at the single-cell level and within its microenvironment.

HTAN Goals

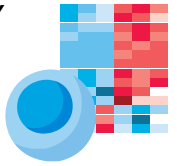
1. MAP TUMOR PROGRESSION

Construct detailed atlases showing how tumors initiate, evolve, and adapt over time, including transitions between states such as precancerous to invasive and treatment-sensitive to treatment-resistant.



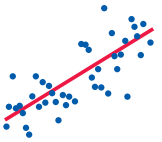
2. CAPTURE TUMOR HETEROGENEITY

Use single-cell and spatial profiling to uncover the diversity of cancer and non-cancer cells in tumors and their microenvironments.



3. ENABLE PREDICTIVE MODELING

Provide open-access data and tools to support computational models that predict tumor evolution and therapeutic response.



Selected HTAN Achievements

- ✓ **ENABLED INTEGRATION WITH OTHER CANCER MOONSHOT PROGRAMS**, such as the Childhood Cancer Data Initiative (CCDI) and Clinical Proteomic Tumor Analysis Consortium (CPTAC), to link tumor biology with clinical outcomes.
- ✓ **CONSTRUCTED 3D ATLASES OF PANCREATIC, LUNG, AND PEDIATRIC BRAIN TUMORS** that map cell types and states in space and time.
- ✓ **REVEALED MECHANISMS OF IMMUNE EVASION AND THERAPY RESISTANCE** in glioblastoma and melanoma.
- ✓ **DEVELOPED HARMONIZED DATA STANDARDS AND DATA PORTALS** to share annotated datasets with the research community.

By visualizing tumors as evolving ecosystems, HTAN is advancing precision oncology and offering new insights into how and when to intervene for maximum therapeutic benefit. Its openly shared atlases are empowering researchers across the globe to decode cancer at unprecedented resolution.

Precision oncology initiatives are increasingly integrating multidimensional profiling into patient care to support real-world clinical decision-making. Large-scale efforts such as NCI's Childhood Cancer Data Initiative (CCDI), United Kingdom's 100,000 Genomes Project, and Australia's Zero Childhood Cancer Program demonstrate how whole-genome, exome, and transcriptome sequencing can inform treatment decisions (160,161). These studies reveal that many actionable biomarkers, including structural alterations, mutational signatures, and RNA expression changes, are only detectable through comprehensive multi-omic analyses. Together, these initiatives are transforming cancer care by enabling more precise, data-driven treatment strategies tailored to the unique molecular profile of each patient.

Collaborative research initiatives, such as the Cancer Grand Challenges, underscore the vital role of integrative research in addressing cancer's most complex and unresolved questions. Launched as a global partnership between the National Cancer Institute (NCI) and Cancer Research UK, Cancer Grand Challenges brings together multidisciplinary teams from around the world to tackle scientific challenges in cancer research too vast for any single laboratory or institution to address (see **Sidebar 14**, p. 49). These challenges focus on critical unmet needs that demand integrated research spanning cancer biology, environmental exposures, and social drivers of health (SDOH), such as determining the cause of early-onset cancers (see **The Growing Population Burden of Cancer**, p. 23), understanding the biology of ecDNA, addressing cancer cachexia (see **Addressing the Challenges Faced by Survivors**, p. 178), developing novel therapies for pediatric cancers, 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 14

Cancer Grand Challenges

Cancer Grand Challenges is a global initiative launched in 2020 by the National Cancer Institute (NCI) and Cancer Research UK 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.

New Challenges

In March 2025, seven new Cancer Grand Challenges were announced. These challenges represent urgent, complex problems in cancer research that international teams are invited to take on; teams submit their proposals, with funded teams to be announced in September 2025.

AI-HUMAN COLLABORATION IN CANCER RESEARCH

Create advanced AI tools that work alongside scientists to generate new cancer research ideas and help plan experiments that can test those ideas in the lab.

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.

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.

TUMOR MICROENVIRONMENT DYNAMICS

Develop methods to study the complex ecosystem surrounding tumors to understand how these components help or hinder cancer growth and treatment.

MECHANISMS DRIVING MUTATIONAL SIGNATURES

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

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.

CANCER AVOIDANCE

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

Active Challenges

Challenges that have a funded team actively addressing them.

- **CANCER INEQUITIES**
- **EARLY-ONSET CANCERS**
- **SOLID TUMORS IN CHILDREN**
- **T-CELL RECEPTORS**
- **CACHEXIA**
- **EXTRACHROMOSOMAL DNA (ecDNA)**
- **NORMAL PHENOTYPES**
- **CANCER CAUSES**
- **MICROBIOTA**
- **TISSUE SPECIFICITY**

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.

As precision oncology advances, it is essential to ensure that its benefits are accessible to all patients. Recent studies emphasize the need to diversify genomic datasets and include ancestral and environmental variables in both research and clinical implementation. Integrating insights from evolutionary biology, more complete references of human genetic variation (pangenomes), and global biobanks are essential to addressing historical biases in cancer genomics and ensuring that biomarker discovery and risk prediction are applicable and effective across diverse populations (162). 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 **Rapidly Delivering Safe and Effective Therapies to Patients**, p. 216).

Reducing the Risk of Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- In the United States (US), about 40 percent of all cancer cases are associated with modifiable risk factors, which necessitates a robust emphasis on and support for public health–focused research.
- The significant decline in cancer mortality over the past three decades is, in part, attributable to reductions in smoking following the implementation of public health campaigns and policy initiatives.
- Nearly 20 percent of US cancer diagnoses are related to excess body weight, unhealthy dietary patterns, alcohol intake, and physical inactivity.
- Vaccination against human papillomavirus (HPV) nearly eliminates the risk of cancers of the cervix, vagina, penis and anus caused by the virus.
- Exposure to high levels of chemicals in the environment, including air pollution, radon, endocrine-disrupting chemicals, and industrial chemicals, can increase an individual's risk of certain types of cancer.
- Workers who are exposed to carcinogens and those who participate in night-shift work are also at an elevated risk of developing certain types of cancer.
- Reproductive and hormone-related factors can significantly influence the risk of developing various cancers, with effects varying by cancer type, timing, and duration of hormone exposure.

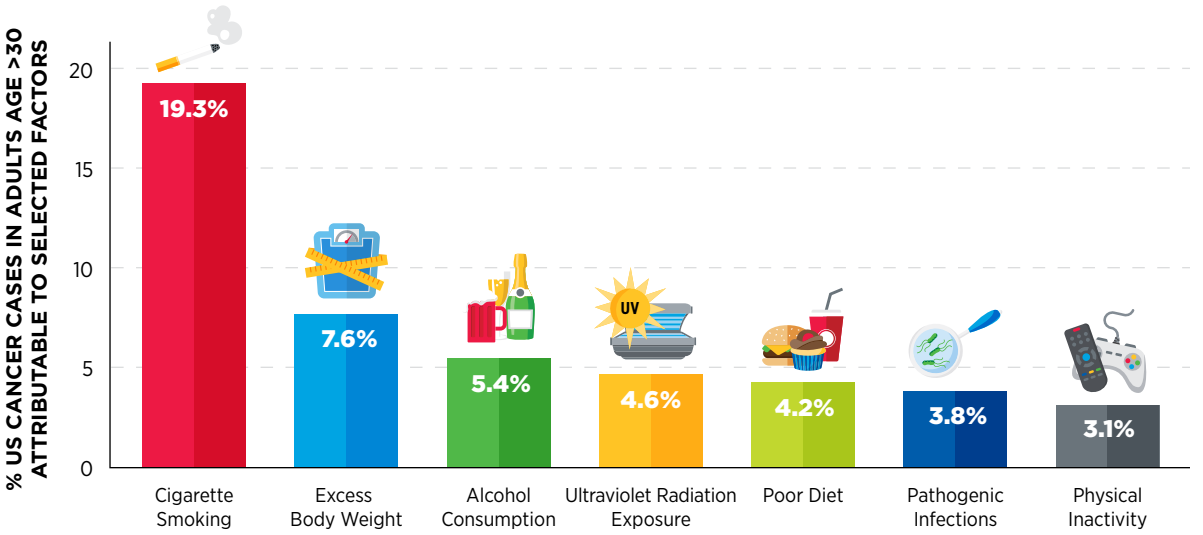
Advances in basic, clinical, translational, and population sciences have significantly expanded our understanding of the factors that contribute to an individual's risk of developing cancer (see **Figure 8**, p. 52). In 2019, an estimated 40 percent of all new cancer cases diagnosed in the United States (US) were attributable to modifiable risk factors including: cigarette smoking, ultraviolet (UV) radiation, excess body weight, alcohol consumption, physical inactivity, and infectious agents (163). Similarly, at the global level, around 40 percent of the total cancer burden is attributed to tobacco use, infectious agents, alcohol consumption and excess body fat (164). Because many of these risk factors are potentially modifiable or manageable, a substantial proportion of cancer cases could be possibly avoided through tailored prevention strategies.

Importantly, while these factors are considered modifiable, they are influenced by social and structural drivers of health (see **Figure 3**, p. 22) and may not always be addressed solely through individual behavior change. For example, individuals experiencing food insecurity—a social driver of health—struggle to obtain a healthy diet. Similarly, those living in unsafe neighborhoods without well-maintained parks face significant barriers to engaging in regular physical activity. To effectively reduce the burden of modifiable risk factors and, in turn, the overall cancer burden, interventions must incorporate both individual- and societal-level strategies.

While our discussion in the following section focuses primarily on behavioral or lifestyle-related risk factors, the

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 reduce 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 preventable risk factors.

Sources: (163,177).

role of psychosocial risk factors should not be overlooked. Psychosocial risk factors, which include depression, anxiety, and stress, have been associated with cancer risk (165,166) and outcomes (167) with mixed findings. However, when examined independently, stress—whether chronic or acute—has been more consistently associated with increased cancer risk (168). Despite this evidence, its exact role remains difficult to determine due to challenges in quantifying stress exposure and controlling stress. In addition, stress may indirectly elevate cancer risk by promoting unhealthy behaviors such as smoking, alcohol use, and poor diet, all of which are well-established risk factors for cancer development.

Increasing evidence shows that stress is not just a trigger for risk-enhancing behaviors but may also act directly on the body by promoting inflammation, disrupting hormone balance, and weakening immune function, all of which can contribute to cancer development and worse outcomes (169,170). As such, stress is gaining recognition as an independent risk factor for cancer initiation and progression (see **Sidebar 15**, p. 53).

In the United States, many of the greatest reductions in cancer morbidity and mortality have been achieved through the implementation of effective public education and policy initiatives. A recent study by the National Cancer Institute (NCI) estimated that approximately 5.94 million cancer deaths were averted from 1975 to 2020 due to public health interventions—including tobacco control programs, national screening, and vaccination programs, as well as advances in treatment (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 218). These gains were primarily seen in cancers for which effective screening methods are available: breast, cervical, colorectal, and prostate cancers (see **Cancer Screening for Early Detection**, p. 71). Lung cancer accounted for the greatest number of deaths averted, largely due to tobacco control efforts (67).

While smoking rates have declined significantly, the increasing prevalence of other risk factors, including obesity among US children and adults and alcohol consumption among adults, remains a significant public health concern (178). In 2018, the most recent year for which data are available, 52.8 percent of US adults reported regular alcohol consumption (179). Compounding these concerns is the underutilization of preventive interventions in the United States, including vaccination against cancer-causing viruses like human papillomavirus (HPV), the primary cause of cervical cancer and certain head and neck cancers.

SIDEBAR 15

Emerging Role of Stress in Cancer Risk

The National Cancer Institute (NCI) defines stress, or psychological stress, as the body's response to physical, mental, or emotional pressure.

How Does Stress Impact Us?

COMMON STRESSORS include everyday responsibilities, such as work, family obligations, and financial concerns.

STRESS AND ITS IMPACT on physical and mental well-being:

- **can be shaped by broader environmental and societal factors**, such as living in conditions marked by poverty, discrimination, or other adverse social drivers of health; and
- **can often lead to individuals adopting unhealthy coping behaviors**, such as smoking, excessive alcohol consumption, physical inactivity, and risky sexual activities—which are all well-established risk factors for cancer.
- **can promote inflammation, disrupt hormone balance, and weaken immune function**, all of which can contribute to cancer development and worse outcomes

What Can Be Done?

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: (171–176).

Harmful contaminants found in air and drinking water, including arsenic, nitrates, disinfection byproducts, and per- and poly- fluoroalkyl substances (PFAS), have been linked to elevated cancer risk (180,181). Additionally, 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 data indicate that certain cancer risk factors are also associated with worse outcomes after a cancer diagnosis, including development of secondary cancers (see **Supporting Cancer Patients and Survivors**, p. 177). In addition, cancer risk factors contribute to other chronic diseases, such as cardiovascular and respiratory diseases and diabetes. Increased recognition of these modifiable risk factors can help local and national public health organizations enhance prevention efforts and lessen the negative health and economic impact of these diseases, including cancer.

Eliminate Tobacco Use

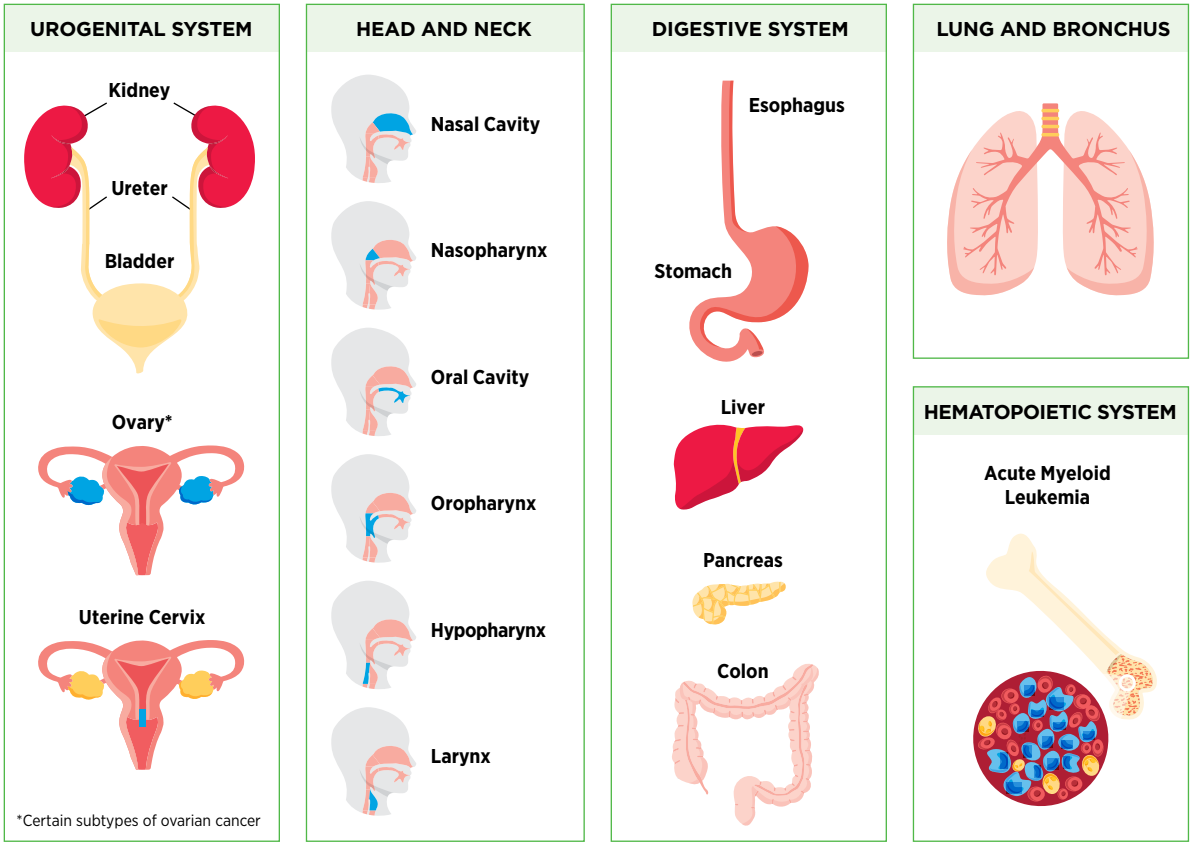
Tobacco use, particularly cigarette smoking, is the leading preventable cause of cancer and is linked to the development of 17 different types of cancer in addition to lung cancer (see **Figure 9**, p. 54). In the United States, cigarette use is responsible for approximately 19 percent of all cancer cases and nearly 30 percent of all cancer-related deaths (163). Between 80 and 90 percent of US lung cancer deaths are attributable to smoking (182). Moreover, cigarette use is associated with a significant reduction in life expectancy, contributing to nearly 10 years of life lost (183).

Research over the past 50 years has demonstrated that byproducts released from smoking tobacco products, such as cigarettes, cause permanent cellular and molecular alterations, which lead to cancer (184–186). Furthermore, smoking causes many other chronic conditions, including chronic obstructive pulmonary disease (COPD), asthma, and many types of cardiovascular diseases, particularly coronary artery disease.

In response to the serious health risks associated with smoking, nationwide tobacco control initiatives have played a critical role in reducing cigarette use among US adults. Smoking rates have dropped from 42.4 percent in 1965 to just 11 percent in 2023 (31,187). Between 2017 and 2023 alone, the number of adults who exclusively smoked cigarettes decreased by 6.8 million. However, this decline was nearly offset by a rise in electronic cigarette (e-cigarette) use in adults (approximately

FIGURE 9

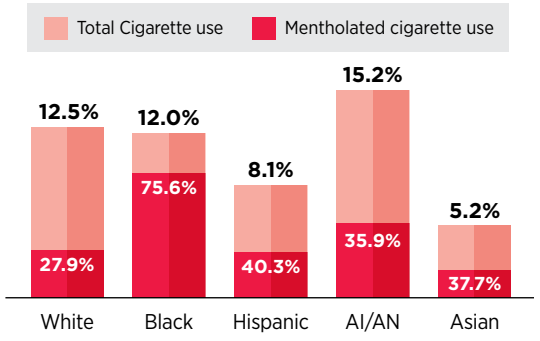
Cancers Caused by Smoking Tobacco



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

Sources: (163,177).

Total and Mentholated Cigarette Use by Race and Ethnicity



Source: (31).

W16

7.2 million) (188). Additionally, in 2023, the most recent year for which such data are available, an estimated 48.6 million US adults reported using any tobacco product (e.g., cigarettes, cigars, and pipes) (188).

There are striking disparities in the use of tobacco products as well as in exposure to secondhand smoke, also a cancer risk factor, as highlighted in the *AACR Cancer Disparities Progress Report 2024*. Overall, current use of cigarettes is higher among males, individuals ages 45 to 64, individuals without a high school diploma, sexual and gender minorities, those who are uninsured or insured by Medicaid, and US residents who live in the South and Midwest (31).

Similar to the trend in adults, tobacco use among US youth—including middle and high school students—is also declining.

15% OF US CANCER PATIENTS ARE CURRENT SMOKERS AT DIAGNOSIS; **STOPPING TOBACCO USE** WITHIN 6 MONTHS OF DIAGNOSIS **CAN ADD AN AVERAGE OF NEARLY 2 YEARS TO A SURVIVOR'S LIFE**

Sources: (196,197).

W17

In 2024, 5.4 percent of middle and 10.1 percent of high school students reported current use of any tobacco product (189). Among high school students, the number of current tobacco users dropped from 1.97 million in 2023 to 1.58 million in 2024, representing 390,000 fewer users. Unlike adults, for whom cigarettes remain the most commonly used tobacco product, e-cigarettes are the most used tobacco product among middle and high school–age youth.

Flavored tobacco products, such as mentholated cigarettes, pose a significant health risk, because they are associated with increased nicotine dependence, lowered smoking cessation rates, and increased mortality compared to nonmentholated cigarettes (187,190,191). In 2020, 43.4 percent of Americans who smoke used mentholated cigarettes, with usage particularly high in Black individuals and young adults ages 18 to 25 years (192). Among middle and high school students, who predominantly use e-cigarettes, 87.6 percent used flavored e-cigarettes, with fruit flavors being the most popular (189).

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 made an attempt, yet only 8.8 percent were successful (193). Smoking cessation yields both immediate and long-term health benefits, especially when cessation occurs at a younger age. Within 10 years of cessation, the risk of developing cancers of the larynx, oral cavity, and pharynx is reduced by half (194,195).

Public health campaigns aimed at banning the sale of mentholated cigarettes and flavored e-cigarettes have been met with mixed responses (198,199). Nonetheless, evidence-based interventions at local, state, and federal levels—such as increasing tobacco prices, implementing public health campaigns, restricting targeted marketing, providing subsidized smoking cessation counseling through insurance, offering FDA-approved medications, and enforcing smoke-free laws—are essential to sustaining the downward trend of tobacco use (see **Flavored Tobacco Products**, p. 222).

Secondhand smoke—the combination of smoke exhaled by individuals who use tobacco products and the smoke emitted from burning tobacco—contains more than 7,000 chemicals, including at least 70 known carcinogens (200,201).

Encouragingly, exposure to secondhand smoke in the United States has decreased, from 27.7 percent during 2009–2010 to 20.7 percent in 2017–2018, the most recent period for which data are available (202). However, exposure remains disproportionately high among some populations. These include children ages 3 to 11 years, regardless of race; non-Hispanic (NH) Black individuals; people with lower income or educational attainment; those living in rental or multi-unit housing; and those employed in blue-collar occupations (203).

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 (189). Recent estimates show that e-cigarette usage was highest among individuals ages 18 to 24 years, with 13.4 percent reporting current use; among these, 71.5 percent of individuals ages 18 to 20 years had never smoked combustible cigarettes (31,204).

In 2024, nearly 6 percent of middle and high school students used e-cigarettes, with 26.3 percent of users reporting daily use of e-cigarettes (205). Among daily users, 87.6 percent reported using flavored e-cigarette products (205). Several factors contribute to the initiation of tobacco use among youth, including the availability of flavored products, targeted marketing, a strong social media presence, and misperceptions about the potential harms of e-cigarettes (189,206).

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 (208,209). Further research is warranted on e-cigarettes and their long-term health effects, especially in teens and young adults so that appropriate preventive interventions can be implemented.

E-cigarette Use in US Youth

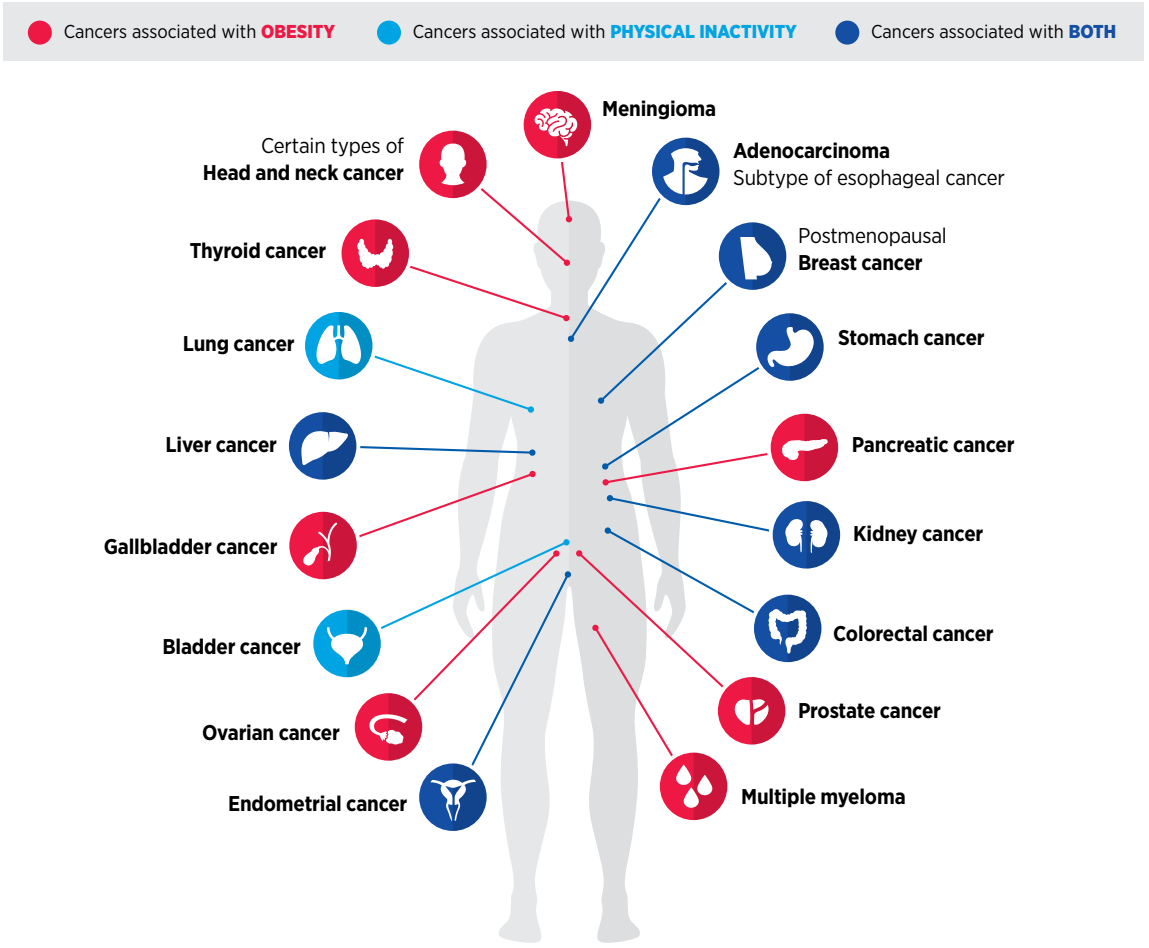
E-cigarette use among US youth declined between 2023 and 2024. Specifically, 3.5% of middle school and 7.8% of high school students reported current e-cigarette use in 2024, down from 4.6% and 10% in 2023, respectively. These reductions represent approximately **390,000 fewer middle school students and 350,000 fewer high school students** using e-cigarettes.

Sources: (205,207).

W18

FIGURE 10

Reasons to Maintain a Healthy Weight and Stay Active



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

Sources: (177,216–222).

E-cigarettes have also become a popular tool for smoking cessation in adults. A recent review found that nicotine-based e-cigarettes increased quit rates by 59 percent compared to nicotine replacement therapy, and by 46 percent compared to non-nicotine e-cigarettes (210). However, more rigorous research, including randomized clinical trials, is still needed to fully understand the effectiveness and long-term efficacy of e-cigarettes as a smoking cessation tool.

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

More than 20 percent of new cancer cases and more than 18 percent of cancer deaths in US adults are attributable to a combination of excess body weight, poor diet, physical inactivity, and alcohol consumption (see **Figure 10**, p. 56)

SIDEBAR 16

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*:

Be physically active as part of everyday life because regular physical activity can decrease risk for nine types of cancer.

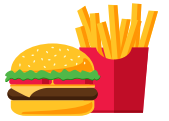
Eat at least 30 g of fiber and at least 400 g of fruit and vegetables each day. A diet rich in vegetables, fruits, whole grains, and beans has a low energy density and promotes healthy weight.

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

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

Get vaccinated against cancer-causing pathogens such as HPV and HBV, where vaccines are available.

Limit consumption of "fast foods" and other processed foods high in fat, simple starches, or added sugars because these contribute to weight gain without providing other nutrients.



Limit intake of red meat (e.g., beef, pork, 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, salami) because these foods can increase risk for colorectal and perhaps other cancers.

Limit alcoholic drinks, if consumed at all, because alcohol consumption can increase risk for seven types of cancer.

Limit intake of sugar-sweetened drinks because these lead to weight gain; drink mostly water.

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

* Greater adherence to these recommendations has 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 (223).

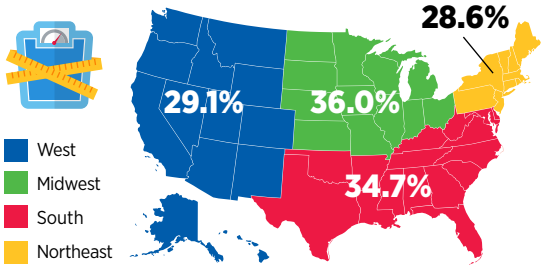
† Overweight and obesity are often assessed using body mass index (BMI): BMI between 18.5 and 24.9 kg/m^2 is considered healthy weight. However, it must be noted that the use of BMI has limitations as it is not an accurate measure of obesity or body fatness for all individuals. Researchers are currently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

Adapted from (224).

(163,211,212). Following a healthier lifestyle—maintaining a healthy weight, being physically active, and consuming a balanced diet—may reduce the risk of developing certain cancers, as well as many other adverse health outcomes (see **Sidebar 16**, p. 57).

Excess body weight is responsible for 7.6 percent of all cancer cases (163). In the United States, the prevalence of obesity among adults was 40.3 percent between 2021 and 2023 (213). High body mass index (BMI) has also emerged as a major risk factor for reduced life expectancy in the United States, ranking among the top five risk factors that lead to a decline in life expectancy for the past 10 years (214). Obesity is not only a national concern but also a global public health crisis, according to the World Health Organization (WHO). In 2022, the most recent year for which global data are available, 43 percent and 16 percent of adults worldwide were classified as overweight and obese, respectively (215). In addition, childhood obesity is on the rise globally, with 8 percent of children and adolescents considered obese in 2022, a fourfold increase from 2 percent in 1990.

Prevalence of Adult Obesity by Region of the United States in 2023



Source: (226). W19

If current trends continue, more than half of the global adult population will be overweight or obese by 2050 (214). To address this crisis, Member States of WHO endorsed the *WHO acceleration plan to stop obesity* at its 2022 World Health Assembly. The plan includes policies aimed at protecting people from the harmful impact of processed food marketing; nutrition labeling (including front-of-pack labeling); fiscal policies (including taxes and subsidies to promote healthy diets); public food procurement and reformulation policies; physical activity; as well as school food and nutrition policies (including school food standards, food provision, and nutrition education) (225).

Emerging data show that weight loss interventions (see **Sidebar 17**, p. 59) can be effective in reducing the risk of cancers associated with obesity (227,228).

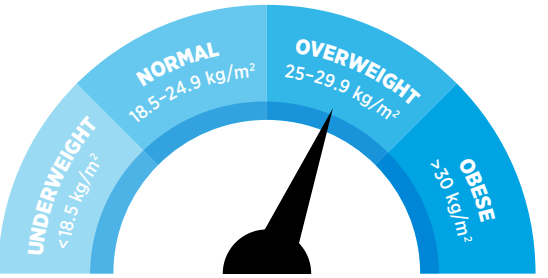
Bariatric surgery is a collection of procedures that when effectively paired with healthy eating and regular exercise may help people who are obese lose weight. Bariatric surgery has also been shown to lower the risk of developing and/or dying from certain obesity-associated cancers by between 37 percent and 65 percent (234). These include cancers of the liver, colon, pancreas, and gallbladder, as well as breast, endometrial, and ovarian cancers in women (234).

Another increasingly popular weight loss strategy is the use of medications, such as semaglutide (Ozempic, Wegovy, Rybelsus) and tirzepatide (Mounjaro, Zepbound), which were originally used to treat individuals with type 2 diabetes mellitus (T2DM). These medications belong to a class of drugs called glucagon-like peptide-1 (GLP-1) receptor agonists, which mimic GLP-1, a natural hormone that helps regulate insulin levels, suppresses appetite, and increases feelings of fullness after eating (238).

When combined with a healthy diet and regular physical activity, GLP-1 receptor agonists have led to significant weight loss for many individuals. A recent study found that BMI and obesity prevalence in the United States declined slightly in 2023 compared to 2022, with the most pronounced decrease in the South—where per capita use of GLP-1 receptor agonists was the highest (239). However, for individuals with obesity, bariatric surgery remains the most effective therapeutic option for achieving substantial and sustained weight reduction (240).

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 kg/m²–34.9 kg/m²
- **Class II:** 35 kg/m²–39.9 kg/m²
- **Class III:** ≥40 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 taking into account factors reflecting 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.

W20

Sources: (229–233).

SIDEBAR 17

Therapeutic Interventions to Reduce Obesity

In the United States, between August 2021 and August 2023, 40.3 percent of individuals 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) = 30–34.9 kg/m²** (Class I obesity) and T2DM with inadequate glycemic control, despite an optimal lifestyle and medical therapy.
- A **BMI = 35–39.9 kg/m²** (Class II obesity) and at least one severe obesity-related comorbidity.
- A **BMI ≥40 kg/m²** (Class III obesity), with or without coexisting comorbidities.

Subcutaneous Injections with Glucagon-like Peptide-1 Receptor Agonists

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

THESE MEDICATIONS ARE RECOMMENDED FOR PATIENTS WITH:

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

Sources: (235–237).

Although the effect of GLP-1 receptor agonists on weight loss is encouraging, more research is required to understand the long-term impact of these medications on reducing cancer risk. Emerging data show that in patients with T2DM, the use of GLP-1 receptor agonists can significantly reduce the risk of esophageal, colorectal, endometrial, gallbladder, kidney, liver, ovarian, and pancreatic cancers, as well as meningioma and multiple myeloma (241). Further, a study comparing bariatric surgery and GLP-1 receptor agonists found that both interventions similarly reduced the risk of developing obesity-related cancers (242). While these findings are promising, it is important to note that no long-term studies of the effects of GLP-1 receptor agonists have been done in the non-diabetic patient population. It will be important to continue monitoring the long-term effects of these weight loss medications in non-diabetic patients, as well as their ability to reduce obesity-related cancers.

A poor diet—high in red and processed meat, low in calcium, fiber, fresh fruits, and vegetables—is attributable to the development of more than 4.2 percent of all cancer cases in the United States. Numerous studies have shown an association between the consumption of highly processed foods and the increased risk of cancer (163,243–245).

Between 2001–2002 and 2017–2018, the consumption of ultra-processed foods among US adults increased significantly, rising from 53.5 percent to 57.0 percent of total dietary intake. During the same period, the consumption of minimally processed foods declined from 32.7 percent to 27.4 percent (246). Approximately 73 percent of the US food supply now consists of ultra-processed products (247). Higher consumption of these foods has been linked to accelerated biological aging—characterized by the gradual accumulation of molecular and cellular damage that impairs physiologic function and increases vulnerability to diseases, such as cancer. Reducing or eliminating ultra-processed foods from the diet may slow biological aging and lower cancer risk (248).

Excessive red meat consumption can increase cancer risk. Intake of red meat specifically should be limited to no more than three servings a week (12 to 18 ounces a week) and should

High levels of red meat consumption were found to significantly **increase the risk of developing liver cancer** by 48%.

Source: (258).

W21

Excess medical cost, loss of work-related productivity, and obesity-related disability payments **cost the US economy $34.7 billion** in 2023.

Source: (275).

W22

not include processed meats (e.g., hot dogs, bacon, and salami), because these foods can increase the risk of colorectal cancers and potentially other cancers including those of the lung, prostate, esophagus, and pancreas (249–259).

Sugar-sweetened beverages (SSB), which include any drink that contains added sugars, such as soda, fruit and sports drinks, and energy drinks, or coffee and tea with added sugars, have also been associated with increased risk of several cancers, such as liver and colon cancers (260–266). Recent data from the Nurses' Health Study found that the consumption of one or more SSB daily has been associated with a four-fold increased risk of oral cavity cancers (267). Further research is needed to assess the relationship of SSB consumption and cancer risk across a more diverse population.

One strategy to lower consumption of SSB is to implement taxes, such as those introduced in several cities in the United States. In cities with such taxes, significant reductions were made in the consumption of SSB compared to cities that did not implement these types of taxes (268–270). As of 2022, eight US jurisdictions and more than 50 counties have implemented tax on SSB (269). However, preliminary data from these counties shows a varying response on the impact the tax has had on BMI and obesity prevalence. As one example, a study examining changes in BMI and obesity prevalence in California cities with SSB taxes—Albany, Berkeley, Oakland, and San Francisco—found no overall change in either measure. However, modest improvements were observed in specific subgroups, particularly among White individuals, women, and individuals ages 20 to 39 (271). Similarly, data from a study of children ages 2 to 18 in Philadelphia showed no significant reduction in BMI or obesity following the implementation of the tax (272). Ongoing evaluation will be essential to understand the long-term effect of these policies on diet, obesity, and cancer risk.

Consumption of a diet rich in fresh fruits and vegetables, nuts, whole grains, and fish can help lower the risk of developing certain cancers and many other chronic conditions (258,273,274). A recent review consisting of over 5 million individuals found that high consumption of fish reduced the chance of developing colorectal cancer by 15 percent (258). One way to increase access to healthy foods is to eliminate food deserts, geographic areas with limited access to grocery stores, to make healthy foods more available. Another strategy is to educate the public about the benefits of nutritious foods in reducing the risk of developing cancer and other chronic illnesses, much like the successful campaigns used for tobacco control. Finally, shifting government subsidies away from commodity crops like corn and soy, which are used to produce added sugars in highly processed foods, toward whole food, minimally processed crops, is essential for promoting healthier diets and reducing the risk 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 indicating that over 46,000 US cancer cases annually could potentially be avoided if everyone met the recommended CDC guidelines for physical activity (see **Sidebar 18**, p. 61) (276,277). One study involving 85,000 participants found that engaging in light-intensity or moderate to vigorous physical activity, lowered the risk of developing cancer by 6 percent and 13 percent, respectively; with sedentary behavior offering no benefit (278). In addition to reducing the risk of developing cancer, incorporating exercise after a cancer diagnosis can improve outcomes (see **Supporting Cancer Patients and Survivors**, p. 177). In a recent study of colorectal cancer patients who received surgery and chemotherapy, 80 percent of those assigned to an exercise program had no evidence of disease, recurrence, or a new cancer diagnosis, compared to 74 percent of patients who received health education alone (279).

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

In the US, **only 13.9%** of adults 65 and older **met federal physical activity guidelines** in 2022.

Source: (280).

W23

SIDEBAR 18

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)

Should be encouraged to move and engage in active play at all levels of intensity throughout the day.

Adolescents
(UNDER 18 YEARS)

Adults
(18–64 YEARS)

Older adults
(65+ YEARS)

	Adolescents (UNDER 18 YEARS)	Adults (18–64 YEARS)	Older adults (65+ YEARS)
Aerobic Activity			
	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

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

Source: (177).

a global scale, WHO's Global Action Plan on Physical Activity offers policy recommendations to encourage active living. These include expanding walking and cycling infrastructure, increasing opportunities for physical activity in schools and workplaces, and enhancing access to recreational spaces. By adopting these strategies, countries can reduce physical inactivity, and the associated health risks.

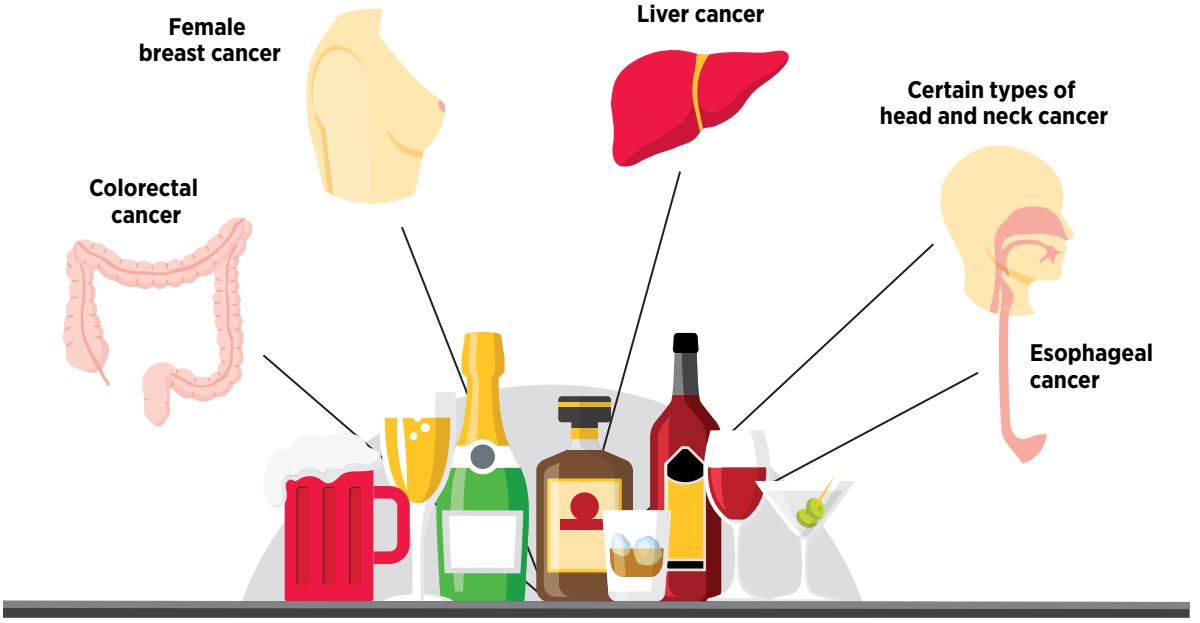
Reduce Alcohol Consumption

Excessive alcohol consumption increases the risk for at least seven different types of cancer (see **Figure 11**, p. 62), and is linked to more than 200 diseases. Ongoing research continues to link alcohol consumption to various cancers; however, larger and more collaborative studies are needed to confirm a causal relationship. 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 (31,163). This translates to about 97,000 cancer cases and 20,000 deaths. It is concerning that according to a recent nationally representative survey, 59.4 percent of Americans did not know that the consumption of alcohol increases the risk of cancer (281).

Limiting alcohol intake has been shown to reduce the risk against developing certain cancers. As an example, an international study consisting of data from 2.5 million patients

FIGURE 11

Alcohol and Cancer Risk



Consumption 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.

from Asia, Australia, Europe, and North America found that with each additional alcoholic drink consumed daily, the risk of pancreatic cancer increased by 3 percent compared to not consuming alcohol daily or at all (282). Alcohol consumption has also been associated with estrogen receptor–positive (ER+) breast cancers, the most common form of breast cancer. A recent review of alcohol consumption and breast cancer found that women who were not current drinkers were 12 percent less likely to develop an ER+ breast cancer (283).

Public messaging campaigns (such as cancer-specific warning labels displayed on alcoholic beverages) along with effective clinical strategies must be considered to reduce the burden of alcohol-related cancers (see **Sidebar 19**, p. 63) (284). One intervention in Canada showed that cancer risk warnings led to a decrease in alcohol sales for labeled products and an overall reduction in alcohol sales by 6.31 percent, indicating that proper labeling can reduce alcohol consumption (285).

GLOBAL BURDEN OF ALCOHOL CONSUMPTION AND CANCER

741,300 CANCER CASES WORLDWIDE

WERE ATTRIBUTABLE TO

ALCOHOL CONSUMPTION IN 2020

W24

Protect Skin From UV Exposure

NCI defines ultraviolet (UV) radiation as invisible rays that are part of the energy released by the sun. UV radiation can also come from artificial sources such as sunlamps and tanning beds. There are three types of UV rays: UVA, which primarily contribute to skin aging and wrinkling; UVB, which are more likely to cause sunburn; and UVC, which are mostly absorbed by the Earth's atmosphere and do not typically reach the surface. Exposure to any source of UV radiation can lead to skin cancers, including basal cell carcinoma, squamous cell carcinoma, and melanoma, the most aggressive form of skin cancer. In 2025, there will be an estimated 104,960 new diagnoses of melanoma of the skin and 8,430 deaths (see **Table 1**, p. 18).

UV radiation accounts for 92 percent of skin melanoma cases and 4.6 percent of all cancer cases (163). UV radiation can damage cellular DNA, with continued exposure leading to

SIDEBAR 19

Guidelines for Alcohol Consumption

The US Department of Agriculture and US Department of Health and Human Services, in the *Dietary Guidelines for Americans, 2020–2025*, advise that people who do not drink alcohol should not start drinking for any reason. There are also some people who should not drink at all, such as those who are pregnant or might be pregnant; 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**.

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.

Source: (177,286).

cancer. Anyone can develop skin cancer, but some individuals are at a higher risk, especially those who are light skinned and those who are sunburned easily. A recent analysis of nationally collected health behavior data found that individuals with a history of severe sunburn—characterized by blistering or peeling—had 3.94 to 4.67 times higher odds of developing melanoma, respectively (287).

A common misconception is that people cannot get sunburned on cloudy days. However, up to 80 percent of harmful UV sunrays can penetrate clouds. It is recommended that individuals

Skin cancer prevalence in US veterans is 9.0% vs. 2.9% in non-veterans. **Veterans have a 72% increased likelihood of having a history of any skin cancer**, and 127% increased odds of melanoma history.

Source: (288).

W25

SIDEBAR 20

Ways to Protect Your Skin

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

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

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

Wear a **wide-brimmed hat**.

Wear **wrap-around sunglasses**.

Apply the recommended amount of a **sunscreen before going outside** (even on slightly cloudy or cool days); it takes about 1 ounce to fully cover the body. 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.

practice sun-safe habits anytime they are outside to limit exposure to harmful UV radiation (see **Sidebar 20**, p. 64).

Indoor tanning exposes individuals to the same harmful UV radiation as sunlight, but in an artificial setting. Among US adults, indoor tanning decreased significantly between 2007 and 2018, from 10 percent to 4 percent. This decline has been largely attributed to legislation aimed at restricting youth access to indoor tanning. As of June 30, 2025, 44 states have legislation regulating tanning bed use by minors (290). Of these, only 20 states and the District of Columbia have complete bans, while the remainder allow use with parental consent. To sustain and accelerate this downward trend, especially among adolescents, states with minimal to no legislation should consider enacting laws that ban indoor tanning for minors.

Across the New England region, **melanoma incidence was lower** in geographic areas farther away from tanning facilities.

Source: (289).

W26

Prevent and Eliminate Infection From Cancer-causing Pathogens

Cancer-causing pathogens (bacteria, viruses, and parasites) increase a person's risk for several types of cancer (see **Table 2**, p. 65). These pathogens may alter cellular function, suppress the immune system, and trigger chronic inflammation, all of which can contribute to cancer development. In the United States, about 3.4 percent of all cancer cases are attributable to infection with pathogens (163). Globally, an estimated 12 percent (2.3 million) of all cancer cases in 2020 were attributable to pathogenic infections, with more than 90 percent of these cases attributable to just four pathogens: human papillomavirus (HPV), hepatitis B (HBV), hepatitis C (HCV), and *Helicobacter pylori* (*H. pylori*) (291).

Individuals can significantly lower their risks by protecting themselves from infection through preventive measures such as vaccination or by seeking treatment to eliminate an infection (see **Sidebar 21**, p. 66).

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 (294). 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 (163). Globally, HPV-related cancers make up about 4.5 percent of all cancers (295).

The HPV vaccine is approved for males and females ages 9 to 45, with recommendations for the first doses beginning at ages 11 to 12. The HPV vaccine currently used in the United States, Gardasil 9, can protect against nine of the cancer-causing HPV strains. To eliminate HPV and its related cancer burden, the national goal is for 80 percent of adolescents to be completely vaccinated for HPV by receiving at least two doses of the vaccine (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 218). Individuals

TABLE 2

Cancer Types and Cancer Cases Caused by Pathogens Globally

Pathogen	Cancer Types Caused by the Pathogen	Cancer Cases
BACTERIA		
Helicobacter pylori	Stomach cancer; non-Hodgkin lymphoma	850,000
PARASITES		
Clonorchis sinesnsis and *Opisthorchis viverrini*	Cholangiocarcinoma	3,500
Schistosoma haematobium	Bladder cancer	N/A
VIRUS		
Epstein-Barr virus (EBV)	Hodgkin lymphoma; certain types of non-Hodgkin lymphoma and nasopharyngeal cancer	156,600
Hepatitis B virus (HBV)	Hepatocellular carcinoma and other cancers	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; non-Hodgkin lymphoma	N/A
Human papillomavirus (HPV)	Cancers of 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	N/A

Sources: (56,177,292,293).

who initiate HPV vaccination at ages 15 to 45 years are recommended to receive three doses.

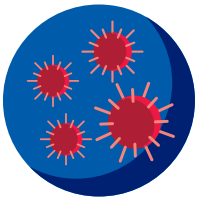
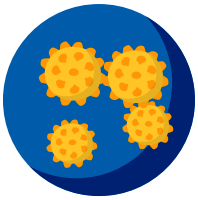
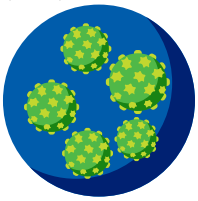
As of 2023, the most recent year for which data are available, only 61.4 percent of adolescents ages 13 to 17 had completed the recommended two dose vaccination series (296). Encouragingly, this number continues to rise because of targeted public health campaigns aimed at increasing awareness and uptake. Reinforcing the value of early vaccination, cervical precancer incidence decreased by 79 percent in individuals ages 20 to 24 (297,298), the group most likely to have been vaccinated when the vaccine was first introduced. However, in adults ages 30 to 44 years, the completion rate for HPV vaccination was only 6.5 percent in 2023 (299), indicating the need for targeted interventions for this age group.

Chronic infection from HBV and HCV can lead to liver cancer and has also been identified as a risk factor for other malignancies, such as 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 (164). In the United States, after new reported cases of HBV remained stable from 2013 to 2019, there was a sharp 32 percent decline in 2020, followed by additional decreases of 14 percent in 2021 and 6 percent in 2022 (300). Although this initial drop was believed to be due to a decrease in health care–seeking behaviors, that is, any action undertaken by individuals who perceive themselves to have a health problem or to be ill, for the purpose of finding an appropriate remedy, and decreased testing during the COVID-19 pandemic, the continued downward trend in 2023 suggests that reductions in HBV transmission may be occurring independently of pandemic-related disruptions (291).

After a decade of increasing rates from 2011 to 2020, HCV rates have stabilized from 2020 to 2023 (301). However, disparities are notable. While acute HCV rates remained steady among NH White individuals between 2022 and 2023, rates among NH American Indian/Alaska Native (AI/AN) individuals rose by 22 percent and were 2.4 times higher than those among NH White individuals in 2023. 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 primary goals are to prevent new infections, improve health outcomes for infected individuals, reduce disparities and health inequities, increase surveillance, and bring together all relevant constituents in coordinating efforts to address the hepatitis epidemic.

SIDEBAR 21

Ways to Reduce Cancer Risk From Pathogens

Pathogen	Ways to Prevent Infection	Ways to Eliminate or Treat Infection	US Recommendations
Helicobacter pylori	Avoid exposure through good hygiene and sanitation	Treatment with a combination of antibiotics and a proton-pump inhibitor can eliminate infection	CDC recommends testing and treatment for people with active or a documented history of gastric or duodenal ulcers, low-grade gastric MALT lymphoma, or early gastric cancer that has been surgically treated
Hepatitis B virus (HBV) 	HBV vaccination Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment of those chronically infected with antiviral drugs rarely eliminates infection but does slow virus multiplication; this slows the pace at which liver damage occurs and thereby reduces risk for liver cancer	Vaccination is recommended as part of the childhood vaccination schedule and is recommended for adults ages 19 to 59 CDC recommends screening for HBV infection in adults 18 years and older at least once in their lifetime using a triple panel test
Hepatitis C virus (HCV) 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment with any of several antiviral drugs can eliminate infection	There is consensus in recommendations from CDC and USPSTF for universal screening of all adults ages 18 to 79
Human papillomavirus (HPV) 	HPV vaccination Practice safe sex, although this may not fully protect against infection	None available	CDC recommends HPV vaccination for boys and girls age 11 or 12 (can start at age 9) to adults up to age 45 years

CDC, Centers for Disease Control and Prevention; FDA, US Food and Drug Administration; MALT, mucosa-associated lymphoid tissue; USPSTF, US Preventive Services Task Force.
Source: (177).

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

Rates of *H. pylori* infection are disproportionately higher among AI/AN communities. A recent study of over 750,000 individuals tested for *H. pylori* between 2000 and 2019 found that positive results were also more likely among older adults; men; individuals who identified as Asian, Black, or Hispanic; those with a non-English language preference; people living in areas with lower levels of college attainment; and individuals who were overweight (302). These findings highlight the need for tailored screening and treatment strategies, particularly in underserved communities who face elevated risk and barriers to health care.

A substantial body of evidence supports the association between chronic *H. pylori* infection and cancer risk. Epidemiologic studies show that people with chronic *H. pylori* infection have increased risk of developing non-cardia gastric adenocarcinoma and that treatment of *H. pylori* infection decreases gastric cancer risk (303). Additionally, nearly all patients who develop MALT lymphoma show signs of *H. pylori* infection, and when these patients are treated with antibiotics, their tumors shrink (304–306). Globally the proportion of cancer cases caused by *H. pylori* infections is highest in South–Central and Eastern Asia, accounting for 69.7 percent of all cases, due to the high prevalence of the infection in these regions (293).

Among those diagnosed with *H. pylori* infection, racial and ethnic minority populations and individuals who smoke are at an even greater risk for developing gastric cancer (307). In the United States, the overall incidence of *H. pylori*-associated gastric cancer declined by 1 percent annually between 2010 and 2019. However, this decline was not consistent across all demographic groups.

Limit Exposure to Environmental Risk Factors

Environmental carcinogens are a class of pollutants that can lead to cancer and are present in the environment, including arsenic, asbestos, radon, lead, radiation, and other chemical pollutants. Exposure to higher than acceptable levels of environmental carcinogens without appropriate protection can increase the risk of cancer. The International Agency for Research on Cancer (IARC) and the US National Toxicology Program are both responsible for evaluating substances and exposures and classifying them as carcinogens at the global and national level, respectively.

Environmental pollutants are encountered in the air, drinking water, and food, making them nearly impossible to avoid. Federal government agencies, including the Environmental Protection Agency (EPA) and HHS, set guidelines for the acceptable exposure limits allowed in the environment (see **Supplementary Table 1**, p. 263). However, some individuals experience higher levels of exposure to certain pollutants due to their living conditions and/or daily activities.

Hazardous materials present in both indoor and outdoor air, as well as in drinking water, can elevate the risk of developing cancer. Air pollution is the contamination of indoor or outdoor environments by chemical, physical, or biological agents that alter the natural characteristics of the atmosphere. Major air pollutants include carbon monoxide, ozone, nitrogen dioxide, sulfur dioxide, and particulate matter (PM), a mixture of solid particles and liquid droplets found in the air. Exposure to these substances has been consistently associated with an increased risk of cancers of the lung (33,35,308,309), breast (310), and, more recently, skin (311).

Drinking water can also contain contaminants including asbestos, arsenic, radon, agricultural chemicals, hazardous waste (316,317), and per- and poly- fluoroalkyl substances (PFAS), a group of endocrine-disrupting chemicals (EDCs) that have been shown to increase the risk of certain cancers, such as thyroid, ovarian, and breast cancers (see **Sidebar 22**, p. 68) (318–320).

In addition to outdoor air pollution and waterborne contaminants, exposure to indoor pollutants also poses a significant cancer risk. Radon is a naturally occurring radioactive gas formed from the breakdown of uranium in soil, rock, and water that can seep into homes through cracks in floors, walls, and gaps around pipes, wires, or pumps. Its levels vary by location and tend to be highest in areas rich in radioactive ore. Moreover, byproducts from previous mining of uranium, for example in the US Southwest, have led to increased levels of radon in nearby areas (323), which disproportionately affect AI/AN tribal communities who live in these areas (324).

Endocrine-disrupting Chemicals

Endocrine-disrupting chemicals can be natural or human-made, and may mimic, block, or interfere with the body's hormones. The use of personal care products, such as hair straightening products, which contain hazardous chemicals with endocrine-disrupting properties have been **associated with increased risk of uterine and early-onset ER+ breast cancers**.

Sources: (312–315).

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SIDEBAR 22

Per- and Poly- fluoroalkyl Substances (PFAS) – The Forever Chemical

Per- and poly- fluoroalkyl 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.

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 stem 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 gone down 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: (321,322).

Radon is the number one cause of lung cancer among people who have never smoked, and is the second leading cause of lung cancer overall, contributing to approximately 12 percent of lung cancers in the United States annually (325–327). To mitigate exposure, individuals should test for radon using approved test kits, which can be obtained, often for free or low cost, through resources listed on the EPA website.

Finally, the effects of climate change, defined as long-term shifts in temperature and weather patterns due to human activity, are an increasing concern among public health experts. Strong scientific evidence confirms that climate change is occurring and suggests that it intensifies exposure to carcinogens via air and water contamination. For example, wildfires in the Western United States and Canada have grown more frequent and severe in recent years due to climate change (328–330) and have led to greater exposure to toxic metals and chemicals (see **Supplementary Table 1**, p. 263). These compounds, found in flame retardants, fire extinguishants, and pesticides, have been linked to cancer risk. A recent study found that firefighters exposed to one such class of compounds, haloalkanes, developed gliomas with tumor signatures associated with this exposure (331).

As rates of lung cancer continue to rise among individuals who have never smoked, growing evidence suggests that air pollution is a contributing factor (33,332–334). One study attributed 1,100 lung cancer cases to air pollution exposure

in the United Kingdom in 2022 (33). Another study found that individuals with lung cancer who have never smoked had significantly higher exposure to air pollution compared to those who were ever smokers (334). New laws, regulations, and policies to reduce the release of pollutants into the atmosphere are urgently needed to reduce the adverse health effects of environmental pollution, including cancer (see **Environmental Justice and Cancer**, p. 224).

Where You Live Matters

Where individuals live can have a big impact on their health, especially when it comes to exposure to harmful chemicals in the air and water. Individuals living near industrial areas may have increased exposure to toxic chemicals and metals. These exposures can increase the risk for certain types of cancer, such as hematologic malignancies as well as thyroid, lung, breast, and uterine cancers (310,318,319,335–338).

Disproportionate levels of exposure to air pollution based on geographic location is another major concern. In 2025, an estimated 156.1 million people were living in geographic areas with unhealthy levels of PM and 77.2 million people living in the United States were exposed to daily, unhealthy spikes in PM. This equates to 12.1 million more people exposed to daily, unhealthy spikes than in 2024 (339). Low-income populations and racial and ethnic minority groups are among those who often experience higher exposure to pollutants (340,341). Those who live in urban areas, particularly those with low socioeconomic status, are exposed to higher levels of certain traffic-related air pollutants, which are associated with an increased risk of breast and lung cancer (337,338).

Public water systems are also a growing concern. In the United States, more than 97 million people are served by public water systems with detectable levels of unregulated contaminants. Notably, these public water systems disproportionately serve counties with higher proportions of Black and Hispanic residents, even after accounting for differences in socioeconomic status and neighborhood disadvantage (342). These findings underscore the urgent need to investigate both regulated and unregulated drinking water contaminants and address disparities in exposure to environmental carcinogens that can have long-term effects.

Where You Work 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 (343). 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.

Other risk factors associated with a person's occupation, including lack of sleep and night-shift work, have also been shown to increase the risk of developing certain types of cancers and other chronic diseases, including diabetes and obesity (344). CDC reports that about 11 million adults in the United States frequently work night shifts. Certain segments of the population are more likely to work these shifts, including men, Black individuals, non Hispanic individuals, and those with only a high school education (345,346).

The body of research on environmental and occupational exposures that increase cancer risk is steadily growing. Collaborative efforts like those led by the Cohorts for Environmental Exposures and Cancer Risks initiative are building the infrastructure to integrate scientific findings and better understand how environmental exposures, along with genetic, behavioral, and structural factors, affect cancer risk across diverse populations. Such efforts are vital to ensuring that interventions to reduce these exposures are implemented equitably.

Be Cognizant of Hormonal Factors

Family Planning, Pregnancy, and Breastfeeding

Studies have shown that a woman's risk of developing certain gynecologic cancers is influenced by reproductive factors, such as oral contraceptive use, pregnancy, and breastfeeding, all of which affect exposure to estrogen and progesterone, hormones produced by the ovaries. Research on oral contraceptive use has found a slightly increased risk of breast and cervical cancer, but a reduced risk of endometrial and ovarian cancer. More recently, one study linked hormonal contraceptive use to an approximately 30 percent increased risk of breast cancer among women who carries mutations in the *BRCA1* gene (347). Additionally, evidence indicates that women who have given birth have a lower risk of developing ER+ tumors compared to women who have never given birth. However, this protective effect is only observed a decade or more after a woman's last pregnancy (348–350).

During the period immediately following pregnancy, women are at an elevated risk of developing pregnancy-associated breast cancers, which are the breast cancers diagnosed during gestation, lactation, and within 5 years postpartum (351). Evidence has demonstrated that both estrogen receptor–negative tumors and triple-negative breast cancer are the most common subtypes of pregnancy-associated cancers (348,350,352). In the United

States, there are about 3,500 cases of pregnancy-associated breast cancer each year (351). Furthermore, the mother's age at pregnancy also influences breast cancer risk. Women who are older when they become pregnant are at increased risk of certain types of breast cancer (353).

Breastfeeding, specifically lactation, has been linked to a reduced risk of breast and ovarian cancers (354–357), with increased duration of breastfeeding associated with a further decrease in risk (350,355,358–360). For example, breastfeeding for 1 to 3 months reduced the risk of ovarian cancer by 18 percent; breastfeeding for more than a year reduced the risk of ovarian cancer by 34 percent (361).

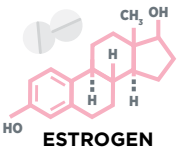
A full understanding of how oral contraceptive use, pregnancy, and breastfeeding influence the risk of female cancers is essential for developing effective risk-reduction interventions.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) refers to treatments that aim to relieve the common symptoms of menopause and the long-term biological changes, such as bone density loss, that take place after menopause. These changes occur owing to 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 undergone a hysterectomy, which is the surgery to remove all or part of the uterus. This approach is used because when estrogen is given alone, but not in combination with progestin, it is associated with an increased risk of endometrial cancer, a type of cancer that forms in the tissue lining of the uterus.

Data show that women who use the estrogen and progestin combination have an increased risk of developing breast cancer (363,364). The risk is greater with longer duration of use and is nearly two-fold higher among women who have used estrogen and progestin in combination for 10 years or longer compared to those who never used HRT (365–367). Women who are no longer using HRT have a lower risk than current users but remain at an elevated risk for more than a decade after they have stopped taking the drugs (366). Individuals who seek HRT should discuss with their health care providers the advantages and possible risks before deciding what is right for them.

Estrogen-based HRT increases both the incidence of and mortality from ovarian cancer. In contrast, combined estrogen-progestin therapy does not increase ovarian cancer risk or mortality and is associated with a reduced incidence of endometrial cancer.

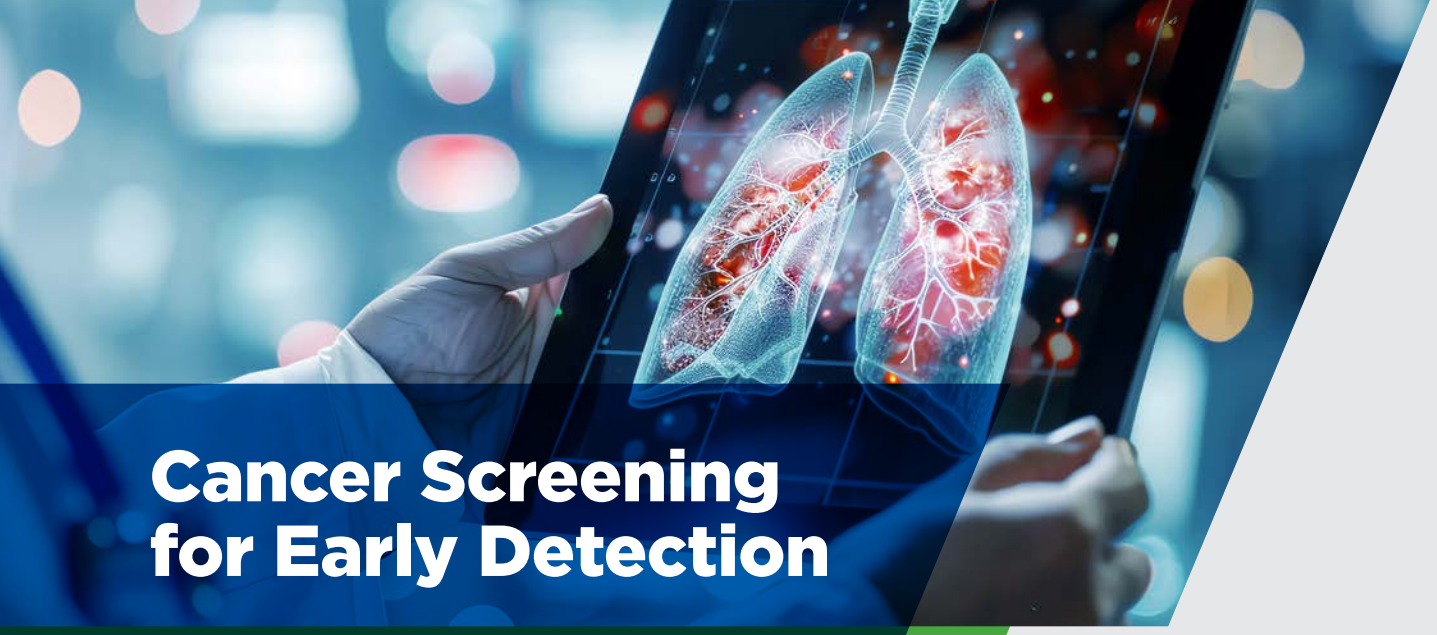


ESTROGEN

Source: (362).

W28

One area of ongoing investigation in hormone replacement therapy is the differential cancer risks among individuals undergoing gender-affirming hormonal therapy (GAHT) (368). Although current data are limited, emerging evidence suggests an increased risk of breast cancer—but a decreased risk of prostate cancer—among transgender women receiving GAHT, compared to age-matched cisgender men (369,370). In contrast, transgender men who received testosterone for at least 5 years showed no increased risk of endometrial, ovarian, vaginal, or vulvar cancers (371). While long-term follow-up studies are needed to more fully understand cancer risks in these understudied and medically underserved populations, current findings provide preliminary guidance for sexual and gender minority individuals considering GAHT (371).



Cancer Screening for Early Detection

IN THIS SECTION, YOU WILL LEARN:

- Cancer screening for early detection means checking for cancer in people who are at an average or increased risk of developing cancer but do not have symptoms of the disease.
- Detecting cancer early through routine screening saves and improves lives and reduces health care costs.
- The US 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 bronchus, and prostate.
- Improving access and adherence to routine cancer screening and follow-up care for all eligible individuals through evidence-based interventions can significantly reduce the burden of cancer.
- Technological advances in artificial intelligence, minimally invasive screening tests, and imaging are fueling optimism for improved approaches to detecting cancers early.

Cancer screening means checking for cancer or abnormal cells that may become cancerous in people who have no signs or symptoms of cancer. Routine screening plays an essential role in reducing the burden of cancer at the population level by detecting precancerous lesions and cancers at the earliest possible stage when they can be treated successfully before developing into advanced-stage cancer that spread to other parts of the body (see **Figure 12**, p. 72).

Routine Cancer Screening Saves Lives

Routine cancer screening helps reduce the overall cancer burden by identifying and treating precancerous changes or early-stage cancers when treatment is more effective and the chance of better outcomes is higher. A study analyzing deaths averted from breast, cervical, colorectal, lung, and prostate cancers between 1975 and 2020 found that screening and prevention collectively prevented 4.75 million of the 5.94 million estimated cancer deaths during that period (67). The impact of each approach varied by cancer type. All of the reduction in cervical cancer mortality was due to screening and treatment of precancerous lesions. In colorectal cancer, 79 percent of lives were saved through screening and removal of precancerous polyps. Screening accounted for 56 percent of deaths averted

SCREENING AND PREVENTION EFFORTS CONTRIBUTED TO

8 IN 10 OF THE NEARLY SIX MILLION LIVES SAVED

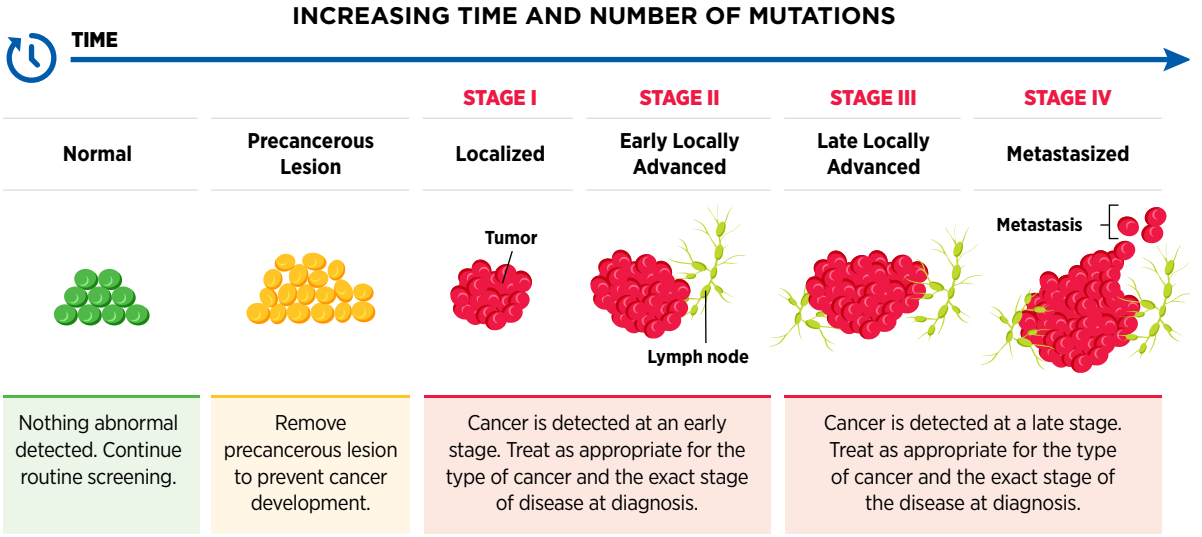
FROM BREAST, CERVICAL, COLORECTAL, LUNG, AND PROSTATE CANCERS BETWEEN 1975 AND 2020

Source: (67).

W29

FIGURE 12

What Can Cancer Screening Find and What Can Be Done?



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, for example, stage I or stage II for a solid tumor, the patient can be treated successfully and has a higher likelihood of better outcomes. If the test finds late-stage cancer, for example, stage III or stage IV for solid tumors, the likelihood of a better outcome decreases 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 (see **Genetic Insights Advancing Cancer Risk Reduction and Interception**, p. 85).

Source: (372).

from prostate cancer and 25 percent from breast cancer, with treatment advances responsible for the remainder. In contrast, nearly all of the lives saved from lung cancer during this time were due to prevention, particularly tobacco control efforts (67).

Another large study showed that a negative result from colonoscopy—one with no signs of cancer or polyps—is associated with lower likelihood of colorectal cancer. A 20-year follow-up of nearly 200,000 people revealed that those with a negative screening colonoscopy had a 49 percent lower risk of developing colorectal cancer and a 44 percent lower risk of dying from it, compared to those who were never screened (373).

Routine cancer screening also reduces the likelihood of disease being diagnosed at a more advanced stage and may help avoid more intensive treatments. For example, a recent study of over 13,000 women ages 70 to 79, who were diagnosed with breast cancer between 2010 and 2017, found that women who had at least one screening mammogram in the 5 years before their diagnosis were 54 percent less likely to be diagnosed at a late stage and 36 percent less likely to die from breast cancer than those who had not been screened. The benefits were even greater for women who had three to four screenings; these women were 37 percent less likely to die from breast cancer compared to those who had one screening (374).

In addition to reducing the burden of cancer at the population level, research is showing that cancer screening also costs less compared to cancer treatment. In 2021, the United States spent $43 billion on initial cancer screening. In comparison,

the cost of the first 12 months of cancer treatment in 2021 was estimated to be $52.56 billion (375).

Routine cancer screening has proven to be one of the most effective tools in reducing cancer mortality, improving survival, and containing health care costs. Continued investment in equitable, evidence-based screening programs not only saves lives but also alleviates the broader burden of cancer on patients, families, and health systems.

Evidence Guides Cancer Screening Recommendations

Panels of subject matter experts—convened by government agencies and professional public health organizations—develop cancer screening recommendations through a structured, evidence-based review process. This report focuses on the recommendations issued by the US Preventive Services Task Force (USPSTF), a congressionally mandated independent panel convened by the Agency for Healthcare Research and Quality, part of the US Department of Health and Human Services (see **Improving Screening Guidelines and Risk-based Approaches**, p. 220). USPSTF provides guidance designed for use in primary care to help prevent disease, including cancer. Its multistep process includes a comprehensive review of the available evidence, as well as engagement with both the scientific community and the public before issuing final recommendations. Other cancer-focused organizations also issue screening recommendations. While specific processes may vary across organizations, all aim to apply the same level of rigor to maximize benefit and minimize harm to public health.

Eligibility Criteria for Cancer Screening

A number of factors determine a person's lifetime risk of developing cancer and eligibility for cancer screening. People without a personal or family history of cancer or a known inherited genetic condition are considered at average risk. For these individuals, screening recommendations are generally based on age and sex assigned at birth.

Certain people have specific cancer screening recommendations because they are at a higher risk of developing cancer than the general population. For example, exposure to cancer risk factors increases the likelihood of developing cancer (see **Reducing the Risk of Cancer Development**, p. 51) and guides screening recommendations, such as those for lung cancer in people who smoke. Individuals who have been diagnosed with cancer (see **Supporting Cancer Patients and Survivors**, p. 177) or those who have multiple immediate family members diagnosed with cancer are also at a higher risk. Similarly, those with hereditary cancer syndromes are at higher risk of developing cancer because of the genetic mutations they carry (see **Figure 6**, p. 36). Experts recommend genetic testing and counseling for people with hereditary cancer syndromes. There are key differences between routine screening to detect cancer at the earliest possible stage, genetic testing to assess the risk of cancer, and diagnostic testing to confirm whether a person has cancer (see **Sidebar 23**, p. 74).

The composition of specific tissues can also influence the risk of developing cancer. For example, research has shown that women with dense breast tissue have a higher risk of developing breast cancer. An analysis of mammograms from more than 33,000 women screened for breast cancer from 2000 to 2018 showed that women with dense breasts were 1.7 times more likely to develop breast cancer than those with less dense breast tissue (376). Having dense breasts is not abnormal but dense breast tissue and tumors both appear white on a mammogram, which can obscure cancer detection. This masking effect prompted the US Food and Drug Administration (FDA) to mandate all mammography facilities to provide patients with information about their breast density. The regulation, finalized in March 2023, went into effect in September 2024 (377). Researchers are actively working to identify approaches that can supplement routine mammography for detecting breast cancer early in women with dense breasts. Women with dense breasts should consider a continued dialogue with their health care providers to stay informed about their potential risk for developing breast cancer.

Some factors that inform cancer screening decisions, such as exposure to cancer risk factors, differ across individuals and can change over time. Furthermore, screening guidelines are revised and updated as new evidence for the benefits or harm of screening comes to light. People should stay informed through regular dialogue with their health care provider and develop a personalized screening plan that reflects their changing risk of developing cancer and tolerance for the potential harms of screening over the course of their lifetime.

Recommendations for Cancer Screening

USPSTF makes screening recommendations for different types of cancer based on whether the benefits outweigh the potential

Uptake of colorectal cancer screening tripled among individuals ages 45 to 49 years after **USPSTF recommended lowering the screening start age from 50 to 45** in 2021.

Source: (378).

W30

SIDEBAR 23

Differences Between Routine Screening, Genetic Testing, and Diagnostic Testing

For distinct reasons, health care providers can recommend different tests to identify people at high risk for developing cancer, to catch precancerous lesions, and/or to detect cancer. The table describes major types of tests for cancer that a health care provider may recommend.

	Routine Screening for Cancer	Genetic Testing for Cancer Risk	Diagnostic Testing for Cancer
WHY IS IT DONE?	To check for cancer and precancerous lesions before symptoms appear.	To find inherited gene mutations that increase cancer risk. Also called germline testing.	To confirm whether someone has cancer.
WHO IS IT FOR?	People without symptoms but who are at average or higher risk of cancer.	People with a strong family history of cancer or known hereditary cancer syndromes.	People who have symptoms of cancer or abnormal results from a screening test.
WHEN IS IT DONE?	At regular intervals (e.g., every year or every few years).	Typically performed in childhood if family history is present.	When there are signs, symptoms, or suspicious findings from a screening test.
WHAT CAN IT FIND?	No abnormalities or a suspicious finding that may need further testing.	Genetic risk for certain types of cancer.	Cancer, and often its type and stage.
WHAT IS THE MAIN BENEFIT?	Can find and remove precancers before they progress or finds cancer early, when treatment is easier and potentially curable.	Can guide prevention, early detection, or risk-reducing interventions.	Can inform treatment decisions.
WHAT IS AN EXAMPLE?	Mammogram to check for breast cancer.	Blood test to check for gene mutations associated with Lynch syndrome.	Biopsy to check for specific tumor markers.

harms. In some cases, USPSTF recommends against screening if the harm is likely to be greater than the benefits or issues an Insufficient Statement indicating there is not enough evidence to make a clear recommendation.

Each USPSTF recommendation is given a letter grade that reflects how strong the evidence is (see **Sidebar 24**, p. 75). This grade also affects whether a screening test is covered without out-of-pocket costs under the Patient Protection and Affordable Care Act (ACA). Sometimes, USPSTF gives different grades for different groups of people for the same type of cancer. All final recommendations and the evidence supporting them are published in scientific journals and on the USPSTF website.

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 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 13**, p. 76).

SIDEBAR 24

USPSTF Guidelines for Cancer Screening

Cancer Type	USPSTF Guidelines*	USPSTF 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 for colorectal cancer is recommended in all adults ages 50 to 75 years.	A
	Screening for colorectal cancer is recommended in adults ages 45 to 49 years.	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 in 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	Periodic prostate-specific antigen–based test, by making a shared decision with the health care provider; recommended for men ages 55 to 69.	C
	PSA-based screening is not recommended in men 70 years and older.	D

hrHPV, high-risk human papillomavirus; LDCT, low-dose computed tomography; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

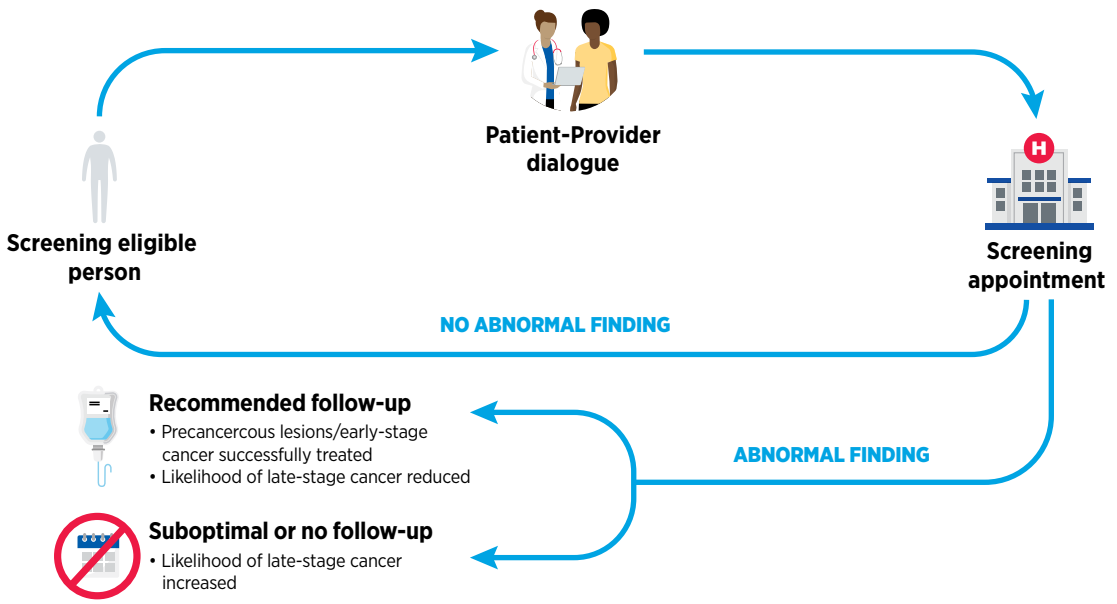
* Indicated here are only USPSTF recommendations for individuals at an average risk of developing cancers of the breast, cervix, colon and rectum, and prostate, or those at a high risk of developing cancer of the lung and bronchus. Several other professional societies issue evidence-based screening guidelines 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 harms outweigh 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 of time. 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.

FIGURE 13

Cancer Screening Is a Continuum



Screening for cancer is a continuum that involves multiple steps, starting with a dialogue with a health care provider, 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.

Tests for Cancer Screening

Cancer screening tests include laboratory procedures that detect cellular or molecular signs of cancer in blood or other biospecimens, as well as imaging or endoscopic procedures that identify tissue changes suggestive of cancer. USPSTF carefully weighs the potential benefits of tests against any risks associated with a given test, ensuring that recommendations will improve public health at the population level (see **Sidebar 25**, p. 77).

Like all medical procedures, screening tests carry some limitations. For example, while complications (e.g., bleeding) from procedures such as colonoscopies are exceedingly rare (379), they are possible. Screening may also yield false-positive results, which can lead to unnecessary follow-up testing, concern and anxiety, or false-negative results, which may delay diagnosis. In some cases, screening may detect slow-growing cancers or medical conditions unrelated to cancer that would not have progressed or caused harm during a person's lifetime. These findings can lead to further testing and interventions that may not always be necessary. Researchers continue to develop new screening tests and improve existing ones with the goal of minimizing potential harm from these tests without compromising their effectiveness in detecting cancer early.

Research Improves the Science of Screening

Cancer screening for early detection is a rapidly evolving field. Many studies focus on evaluating the real-world impact of recommended screening tests and identifying ways to reduce potential harm from routine screening. As one example, a recent study of over 10,000 patients found that the USPSTF-recommended fecal immunochemical test (FIT) for colorectal cancer screening reduced the risk of dying from colorectal cancer by 33 percent among study participants (380), indicating the impact of easy-to-use screening tests on reducing the burden of cancer. A second study found that adjusting the test to be more sensitive helped find 8 percent more cases of colorectal cancer without increasing false-positive test results, making it affordable to improve noninvasive colorectal cancer screening (48). A study from the Netherlands found that at-home stool tests could safely replace follow-up colonoscopies after polyp removal without missing serious cases (381), thus reducing the use of an invasive screening test. Using annual FIT reduced the number of follow-up colonoscopies by up to 41 percent and still effectively detected advanced colorectal cancer (381). Another recent study found that, compared to receiving multitarget DNA tests (see **Sidebar 25**, p. 77) or blood-based

SIDEBAR 25

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. Tests described below are a part of evidence-based cancer screening recommendations by USPSTF.

	USPSTF-recommended Test*		
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 (or 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 smear (Pap test)	Cytologic test	Looks for abnormal cells in the cervix that may turn into cancer.
	hrHPV test	Molecular test on cervical sample	Detects hrHPV types that cause cervical cancer.
COLORECTAL	FIT	Stool test	Checks for a product of red blood cells in stool that can be a sign of cancer.
	High-sensitivity gFOBT	Stool test	Detects a product of red blood cells in stool that may signal colorectal cancer.
	Stool DNA-FIT	Stool test	Looks for cancer-related DNA changes and a product of red blood cells in stool.
	Colonoscopy	Endoscopic imaging	Uses a camera-tipped tube to check the entire colon for cancer or polyps.
	Flexible sigmoidoscopy	Endoscopic imaging	Checks for cancer or polyps in the lower part of the colon.
	CT colonography (virtual colonoscopy)	Imaging	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; hrHPV, high-risk human papillomavirus; LDCT, low-dose computed tomography; 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 determine 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.

Source: (177).

In 2021, the second year of the COVID-19 pandemic:

- **Cancer diagnoses nearly recovered to the pre-pandemic time** but remained below expectations by 4.9% in rural areas.
- **Lung and prostate cancer cases** were also **24,940 and 14,104 fewer**, respectively, than estimated.

Source: (383).

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tests every 3 years, annual FIT was most effective in low-resource community clinics, yielding 121 life-years gained per 1,000 screened individuals and a net monetary benefit of $5,883 per person (382). Together, these findings support using at-home stool tests for colorectal cancer screening in reducing the burden of disease at the population level, and suggest that the test may be more cost-effective for screening and follow-up care than alternatives, especially in low-resource settings and for large-scale screening programs.

Researchers continue to evaluate the public health impact of existing screening recommendations and to identify aspects that can be improved further. A large national study of more than two million women evaluated the impact of the 2009 change to USPSTF breast cancer screening guidelines recommending biennial instead of annual mammograms for women under 50. Although less frequent mammograms led to a decline in early-stage breast cancer diagnoses from 2004 to 2019, this decline did not result in an increase in more advanced cancers, as experts had feared (384,385). Of note, overtreatment, i.e., surgeries to remove an entire breast, decreased following the revised recommendation (384).

USPSTF recommends a screening colonoscopy every 10 years after a colonoscopy with negative results. One recent study analyzed colonoscopy data from the past 40 years while taking into account personal risks and found that some individuals with a low risk of developing colorectal cancer can safely wait longer than 10 years for their next colonoscopy (373). The findings of this study highlights the positive impact of evidence-based screening recommendations and identifies areas in which further improvements are possible.

A **new test** that identifies a product of blood and cancer-linked DNA changes in stool **detected 95% of colorectal cancers** and **57% of advanced precancerous polyps** with high accuracy even for early-stage disease.

Source: (386).

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Assessing newer and improved screening methods is another area of active research. For example, new findings are adding to growing evidence that digital breast tomosynthesis (DBT), an advanced form of three-dimensional mammography, may help detect breast cancer earlier and reduce the number of more serious, late-stage cases (387). A study of more than 270,000 screenings found that DBT identified more cancers than standard digital mammography (DM) and did so with fewer false-positive results (388). More importantly, the study found that among invasive cancers—those that have spread to nearby tissues—the proportion classified as advanced cancers—those that have spread to other organs extensively—was lower with DBT compared to DM (32.6 percent vs. 43.6 percent). This difference was even more striking during repeat screening (29.1 percent with DBT compared to 44 percent with DM), indicating that regular screening with DBT could lead to less likelihood of being diagnosed with more advanced cancers (388). In another study of over 208,000 women with a family history of breast cancer, DBT significantly outperformed DM by reducing false positives and unnecessary follow-ups. It also found fewer advanced cancers in women with extremely dense breasts, indicating that more aggressive tumors are diagnosed at an earlier stage (389). Although potential concerns about overdiagnosis and equitable access to Black and Hispanic women remain, these findings indicate that DBT is superior in catching cancers earlier, especially in high-risk women, potentially reducing the need for more aggressive care.

Collectively, studies discussed here exemplify how new research improves early detection of cancer through development of smarter tools and more personalized strategies. These advances are helping make cancer screening more effective, efficient, and patient-centered.

Effective Strategies Increase Screening Uptake

Getting screened for cancer according to recommendations is one of the most effective ways to reduce cancer deaths, yet many people in the United States are not up to date on their screenings (see **Table 3**, p. 79). Screening rates are especially low among certain groups, including racial and ethnic minorities, residents of sovereign Native Nations, and people with limited access to health care (12). Suboptimal uptake of routine screening also means getting screened when it is not necessary. A recent study found that it can take up to 13 years

TABLE 3

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

Cancer Type and Most Recent Data Year*		Breast (2023)	Cervical (2021)	Colorectal (2023)	Lung (2022)	Prostate (2023)
OVERALL		**80**	**73**	**60**	**17**	**37**
RACE AND ETHNICITY	AI/AN only or multiple	74	65	55	14	23
	Asian only	81	62	54	23	26
	Black only	86	72	62	18	34
	Hispanic	78	66	52	17	27
	White only	79	78	63	17	41
SOGI	Bisexual	†	78	60	N/A	†
	Gay or lesbian	80	69	71	N/A	54
	Heterosexual	80	74	60	N/A	37
INCOME	>200% FPL	83	77	63	18‡	41
	<100% FPL	69	63	47	19§	21
EDUCATION	College graduate	85	83	68	17	48
	Less than high school	70	56	48	15	22
INSURANCE STATUS	Medicaid/Public/Dual eligible	72	68	56	16	22
	Medicare (≥65 years)	83	57	80	26	46
	Private	83	77	65	14	38
	Uninsured	50	55	23	4	13
IMMIGRATION STATUS	Born in US/US territory	80	76	63	N/A	39
	In US 10+ years	81	66	53	N/A	30
	In US fewer than 10 years	66	53	37	N/A	†

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

* Breast cancer: Estimates represent the 2016 USPSTF age eligibility recommendations (50 to 74 years), as the 2024 USPSTF age eligibility recommendations (40 to 74 years) were not in place at the time of the survey from which these data are derived. Cervical cancer: Estimates are from women ages 21 to 65. Colorectal cancer: Estimates are from US adults ages 45 to 74. Lung cancer: Estimates are from US adults ages 50 to 79. Prostate cancer: Estimates are from men age 50 and older.

† Estimates are statistically unstable and not shown.

‡ Income level ≥$75K.

§ Income level <$25K.

Source: (39).

or even longer for unnecessary and potentially harmful cancer screenings to decline in use after new guidelines are introduced (390). This is concerning because unnecessary screenings can potentially lead to overdiagnosis and other issues, such as anxiety associated with medical procedures.

If the initial screening test suggests cancer, it is important to confirm the result with a follow-up test (see **Figure 13**, p. 76). Unfortunately, certain population groups in the United States continue to experience low adherence to routine cancer screening and follow-up care because of multilevel factors, including systemic and structural racism, lack of access to quality health care, minimal or no awareness of the benefits of routine cancer screening, and mistrust in the health care

Three in 10 screening-age US adults were **more than a year behind on recommended cancer screening** in 2025.

Source: (391).

W33

SIDEBAR 26

Disparities in Adherence to Routine Cancer Screening and Follow-up Care

Several segments of the US population experience disparities in the uptake of routine cancer screening, as well as in the receipt of follow-up care when the initial cancer screening test finds possible signs of cancer. Examples presented here from recent studies highlight these disparities:

44% less likely	Black women were 44 percent less likely than White women to receive same-day follow-up care after abnormal screening mammography (394).
2X less likely	Women without a high school education were two times less likely than college graduates to adhere to cervical cancer screening (395).
66% less likely	Uninsured individuals were 66 percent less likely than those with insurance to get lung cancer screening (396).
5X farther	Residents of the American Indian/Alaska Native–majority areas lived more than five times farther from a lung cancer screening facility compared to residents of non-Hispanic White–majority areas (397).
Only 59%	During 2019–2021, only 59 percent of women ages 40 to 49 were up to date with mammography screening (398).
TWICE as likely	Bisexual/queer women were twice as likely as straight women to be uninsured and 9 percent less likely to be up to date with mammography (399).
15% vs. 60%	Only 15 percent of screening-eligible residents of US-affiliated Pacific Islands were up to date with colorectal cancer screening compared to 60 percent of screening-eligible residents of the contiguous United States (400).

system (see **Sidebar 26**, p. 80). For example, Black adults are 15 percent less likely to receive the follow-up colonoscopy after an abnormal stool-based test (392). New research shows that if the rates of follow-up colonoscopies as well as polyp detection by endoscopists—the health care professional who performs colonoscopies—were the same in Black adults as in White adults, colorectal cancer deaths in the Black population could drop by 19 percent (393). These findings underscore the importance of follow-up care and its quality in reducing the population-level burden of cancer.

It is important to understand whether low rates of cancer screening and follow-up care are part of the reason why some population groups experience higher cancer burden. One way to improve screening is to design care that meets the unique needs of different communities and helps overcome barriers, such as cost, access, or mistrust of the health system. It is also crucial that screening guidelines and programs are based on data that reflect the specific populations they are meant to serve.

Reducing Structural Barriers

Structural barriers to health care access, such as lack of nearby health care facilities, health insurance, and public transit, play a significant role in low adherence to cancer screening and follow-up care. Research shows that reducing structural barriers to health care can increase participation in routine cancer screening and follow-up care. For example, multiple barriers to colonoscopy participation have been

A **multistep intervention** that included mailed test kits, text- and email–based reminders, and clinic-based support **increased colorectal screening uptake in adults** ages 45–49 by **nearly seven times**, compared with uptake before the intervention.

Source: (403).

W34

identified, including access to nearby health care facilities, lack of provider recommendation, and lack of knowledge and awareness (401). A 20-year colorectal cancer screening initiative in California addressed structural barriers through a systematic outreach that included reminding individuals who were overdue for colorectal cancer screening. People had the option to be sent FIT kits for at-home tests. The initiative more than doubled screening rates from 37 percent to 80 percent across 1.1 million adults, leading to a 30 percent drop in cancer incidence and a 50 percent decline in deaths. Furthermore, the program also sharply reduced racial disparities in outcomes, cutting colorectal cancer mortality among Black patients by over half (402).

Lung cancer screening is another example in which lack of access to specialized facilities and trained staff poses major structural barriers to participation in routine screening and follow-up care. Only 17 percent of eligible US adults were up to date with lung cancer screening in 2022 (see **Table 3**, p. 79). Researchers are working to identify ways that can increase participation of eligible individuals in lung cancer screening. A review of 12 global studies found that mobile lung cancer screening units using low-dose CT scans are a powerful way to detect lung cancer early, especially in rural, low-income, and uninsured communities (404). Across programs in the United States, the United Kingdom, Japan, China, and Brazil, mobile screening units detected 80 percent of lung cancers at early, more treatable stages. These findings support expanding mobile screening to save lives, increase adherence to screening recommendations, and reduce health disparities (404).

Researchers are finding that similar approaches are effective for breast cancer screening, which also requires specialized facilities and trained staff to perform mammography. A national study of over 2.6 million women on Medicare fee-for-service plans found that mobile mammography helped reach underserved women—especially those living in rural areas, lower-income communities, and among American Indian/Alaska Native (AI/AN) populations. While only 0.4 percent of women used mobile mammography, those who did had significantly fewer years without a mammogram compared to those who used only facility-based services. Mobile mammography was over five times more likely to be used by AI/AN women and three times more likely among rural residents (405). These findings show that mobile units are helpful ways to expand access for population groups who might otherwise go unscreened for lung and breast cancers.

Examples highlighted here underscore the effectiveness of innovative approaches—such as mailed test kits and mobile screening units—in expanding access, increasing early detection, and narrowing disparities across cancer types. These interventions can save lives and reduce or eliminate disparities in cancer prevention.

Integrating Patient Navigation

Patient navigation refers to personalized, one-on-one support that helps individuals overcome logistical, financial, and informational barriers—such as scheduling appointments, understanding test results, and securing transportation or insurance coverage (see **Sidebar 52**, p. 191). Patient navigation has been effective across the cancer care continuum, including increasing participation in routine cancer screening and follow-up care and reducing disparities (406).

A recent study involving 260 individuals experiencing homelessness showed that patient navigation significantly increases lung cancer screening participation. Patient navigation increased screening completion by nearly five-fold, with 43 percent of participants completing lung cancer screening within 6 months compared to only 9 percent without navigation (407). A review of 18 studies found that patient navigation—using bilingual community health workers to guide individuals through the screening process—significantly improved screening rates for breast, cervical, and colorectal cancers (408). In some settings, colorectal screening increased from 11 percent to 90 percent, and cervical screening rose from about 2 percent to 60 percent (408). Together, these studies underscore patient navigation as a highly effective strategy to

Compared to usual care, **mailed FIT outreach with patient navigation tripled the completion rate of colorectal cancer screening** and improved follow-up colonoscopy rate by 55% among those with positive FIT results.

Source: (409).

W35

enhance screening uptake as well as address disparities in early cancer detection.

Another recent study examined the impact of implementing patient navigation in a safety-net setting to improve cervical cancer screening. Approximately 2,500 women ages 30 to 65 who were overdue for cervical cancer screening were enrolled in a randomized controlled trial to evaluate the impact of patient navigation on participation of underserved women in cervical cancer screening (410). Participants, 67 percent of whom were from underserved communities, received either telephone reminders for screening at the clinic, telephone reminders along with a mailed self-collection HPV test, or telephone reminders, mailed self-collection HPV test, and patient navigation. Researchers found that the introduction of patient navigation increased participation from 17 percent among those who only received a telephone reminder to 47 percent (410). These results highlight patient navigation as essential for reducing cervical cancer disparities in underserved communities.

Collectively, the examples discussed above show that patient navigation is a powerful tool for improving access to cancer screening, particularly among underserved and high-risk populations. As cancer screening guidelines evolve, embedding patient navigation into care delivery models will be key to improving equity in early detection (see **Advancing Policies to Strengthen Cancer Prevention and Screening Programs**, p. 218). This point is reinforced by the President's Cancer Panel's report, *Enhancing Patient Navigation with Technology to Improve Equity in Cancer Care*. The report, released in November 2024, underscores the importance of patient navigation in cancer care and recommends implementing technologies to connect patient navigators with cancer patients (411).

Engaging Communities

Evidence shows that community engagement and tailored approaches are highly effective in increasing participation in cancer screening and follow-up care, especially among medically underserved populations (412). A national study of nine breast and cervical cancer screening programs found that partnerships between clinics and community-based organizations, such as churches, shelters, radio stations, and cultural centers, played a crucial role in reaching medically underserved women (413). Researchers have also found that members of closely connected communities are more likely to be up to date on routine screenings, even in the absence of consistent access to health care. This observation presents a powerful opportunity: When one person in a tightly knit community has a positive screening experience, they often share it with others. Because trust runs high within these networks, such word-of-mouth can spur broader uptake, making tailored, community-based interventions especially impactful. For instance, a recent study found that Mexican immigrant women living in rural areas had higher mammography rates (54.4 percent) than those in urban areas (45.6 percent) (414). These differences were linked to stronger family ties and traditional beliefs that supported health-seeking behaviors. Similarly, another study found that Black immigrant women with stronger social ties were nearly three times more likely to be up to date on cervical cancer screening (415). These findings underscore why community-based strategies can be so powerful in improving screening uptake.

Real-world interventions reinforce this evidence. In Central Texas, a lung cancer screening program combined bilingual outreach with patient navigation to screen more than 600 high-risk adults (416). From 2020 to 2023, 83 percent of patients who agreed to screening completed it—regardless of race, age, or insurance status. Nearly half of current smokers in the program received help for smoking cessation, and one in three reported success. The program demonstrates how culturally tailored, community-based interventions can eliminate barriers to routine screening, which can save lives. Community-based strategies have also proven effective for informed decision-making. A review of clinical trials found that tailored educational interventions, delivered through health care settings and churches, helped Black men make more informed decisions about prostate cancer screening (417). These programs used group discussions and decision-making tools to improve knowledge and readiness to act.

Together, these studies show that engaging trusted community leaders, organizations, and peers fosters trust and strengthens ties to the health care system. Tailored strategies, such as culturally relevant education, language-specific materials, and flexible service delivery, can bridge gaps in cancer screening and lead to better outcomes for all population groups.

Technological Innovations Advance Cancer Screening for Early Detection

Driven by innovative research, advances in molecular diagnostics, artificial intelligence (AI), and minimally invasive screening approaches are enabling earlier and more precise cancer detection. Here, we highlight four areas in which rapid progress is poised to further transform cancer early detection.

Advances in Artificial Intelligence (AI)

AI is the ability of a computer to perform tasks commonly associated with human intelligence, such as how to act, reason, and learn. The use of AI in cancer screening for early detection is rapidly advancing, with research fueling innovations that are reshaping how cancers are identified and diagnosed. These advances are already reflected in the growing number of

TABLE 4

A Selected List of FDA-approved AI-assisted Medical Devices and Software in Cancer Early Detection (July 1, 2024–June 30, 2025)*

Approved In	Name	Cancer Type	How It Is Used	What It Looks For
August 2024	qCT LN Quant	Lung	Runs on routine chest CT scans	Tiny lung spots (nodules) that may become cancer
September 2024	CADDIE CADe	Colorectal	Enhances visualization during colonoscopy	Suspected polyps that can turn into cancer
November 2024	ProFound Detection V4.0	Breast	Works with 3D mammograms	Breast areas that could be cancerous
	Transpara 2.1.0	Breast	Works with 2D or 3D mammograms	Highlights breast regions that look suspicious
February 2025	Ibex Prostate Detect	Prostate	Analyzes prostate biopsy images	Generates heatmaps to help pathologist identify missed tumors
March 2025	F.A.S.T. aiCockpit CT Lung Nodule	Lung	Adds AI findings to chest CT scans	Finds and measures lung nodules

2D, Two-dimensional; 3D, Three-dimensional; AI, Artificial intelligence; CT, Computed tomography; FDA, US Food and Drug Administration.

* This table is not an exhaustive list of every AI-assisted tool approved by FDA during the 12-month period covered in this report.

FDA-approved AI-assisted tools designed to enhance cancer screening and diagnosis (see **Table 4**, p. 83).

Recent studies demonstrate the transformative potential of AI in improving how breast cancer is detected, while also reducing the workload of radiologists. A large Swedish screening trial involving over 100,000 women showed that AI-assisted mammography detected 29 percent more cancers without increasing false positives, which are cases in which a test incorrectly indicates that a person has cancer when they do not. In addition, it led to a 44 percent reduction in the number of screenings requiring radiologist review (418). In a randomized controlled trial, AI triage reduced time from mammogram to biopsy by 30 percent—nearly 17 fewer days—with no missed cancers (419). Another study, involving nearly half a million women, found that using AI to support mammogram interpretation improved breast cancer detection by nearly 18 percent (420).

A US-based study using magnetic resonance imaging (MRI) found that an AI model could predict breast cancer up to 1 year in advance, even when radiologists saw no abnormalities (421). The AI system correctly identified 30 percent of cancers before diagnosis and flagged the correct location in over half of those cases. Another large study of racially and ethnically diverse women that used current as well as up to 4 years of prior mammograms to train an AI model for predicting a woman's risk of developing breast cancer found that this approach markedly improved accuracy of the model (422). These findings offer a powerful tool for high-risk populations such as women with dense breasts, for whom many organizations recommend receiving MRI to supplement mammography (423). Together, these studies support a future in which AI helps detect breast cancer earlier and more precisely without overwhelming health care systems.

AI-assisted tools are also revolutionizing colorectal cancer detection. Two recent studies offer strong evidence that AI significantly improves polyp detection during colonoscopy, a key factor in preventing colorectal cancer. An analysis of 28 screening trials with over 23,000 participants found that AI-assisted colonoscopy improved polyp detection rates by 20 percent and reduced the rate of missed polyps by 55 percent (425). However, the improvements were primarily for small, low-risk lesions, suggesting the need for further refinement.

In June 2025, the US Food and Drug Administration authorized **CLAIRITY BREAST**, a platform that uses **AI to predict a woman's 5-year future risk of developing breast cancer** using only the existing screening mammogram.

Source: (424).

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TABLE 5

FDA-approved Minimally Invasive Tests and Devices for Cancer Screening for Early Detection (July 1, 2024–June 30, 2025)

Approved In	Name	What It Is	What It Does
July 2024	Shield	Blood test	Screens for colorectal cancer by detecting cell-free DNA shed by tumors into the bloodstream
October 2024	Cologuard Plus	Stool test	Detects blood proteins and DNA changes linked to colorectal cancer in stool samples
May 2025	Teal Wand	Self-collection device	Enables at-home vaginal sample collection for cervical cancer screening*

FDA, US Food and Drug Administration.

* Researchers are exploring additional strategies to expand access to cervical cancer screening through at-home sample collection. One such effort is the SHIP trial, a National Cancer Institute–funded study designed to evaluate whether self-collected vaginal samples for HPV testing yield diagnostic accuracy comparable to clinician-collected cervical samples. If the trial confirms equivalent performance, self-sampling could offer a viable alternative that enhances screening uptake by addressing common barriers such as discomfort, inconvenience, or limited access to clinical settings (430).

In another study from the United Kingdom involving 2,000 patients, the FDA-approved GI Genius AI module improved detection of small, high-risk polyps that often go unnoticed. These benefits were observed in patients both with and without symptoms, indicating real-world utility across screening populations (426).

Although AI holds immense promise for transforming early cancer detection, experts caution against rapid adoption without addressing potential risks (see **New Advances in Artificial Intelligence**, p. 194). A recent review of 11 studies involving nearly 20,000 patients found that AI-based tools improved lung cancer detection by up to 20 percent, but also increased false positives—potentially leading to unnecessary follow-up scans and anxiety (427). Many current AI models are trained on nondiverse or low-quality datasets, which may limit their performance in underrepresented groups, such as patients with rare cancer subtypes or dense breast tissue (428).

Ensuring that AI lessens, not worsens, disparities in cancer care requires continued investment in research as well as better data diversity and regulatory oversight (see **New Advances in Artificial Intelligence**, p. 194). While AI technology is advancing quickly, careful implementation is essential to maximize benefits and minimize unintended harms.

Advances in Minimally Invasive Screening Approaches

Catching cancer early saves lives but most traditional screening tools, such as the Pap test, mammogram, or colonoscopy, either apply to only a few cancer types or require invasive procedures (see **Sidebar 25**, p. 77). In the 12 months covered in this report, several new minimally invasive tests and devices have been approved by FDA, reflecting the rapid pace of innovation in this field (see **Table 5**, p. 84).

Several recent studies underscore the promise of minimally invasive tests in detecting colorectal cancer early. One study using samples from patients with colorectal cancer found that a next-generation stool DNA test correctly identified 95 percent of colorectal cancers and over 57 percent of advanced precancerous lesions (386). Another study evaluated a new blood test that detected more than 80 percent of early-stage colorectal cancers, while producing fewer false positives than standard methods (47). Both tests received FDA approval in 2024 (see **Table 5**, p. 84).

Beyond tests for early detection of individual cancers, researchers are also developing multi-cancer early detection (MCED) tools that can detect multiple cancer types by analyzing molecular markers, such as circulating tumor DNA (ctDNA) shed by cancer cells. These mostly blood-based tests

Results from self-collected samples for **cervical cancer detection using the Teal Wand** device matched results in clinician-collected samples in 95% of cases—and **identified serious cervical changes just as reliably**. FDA approved the kit in May 2025.

Source: (429).

W37

A **new enzyme-based blood test accurately detected 85% of early-stage pancreatic cancer cases**, a disease that often goes undetected until cancer has progressed to an advanced stage.

Source: (432).

W38

offer the potential to simplify cancer screening by identifying a wide range of cancers, including those without current screening methods.

Minimally invasive screening aims to detect multiple cancers before symptoms arise. A large international study tested a blood-based MCED method that analyzed DNA methylation patterns in cell-free DNA (cfDNA), which are fragments of DNA shed by normal and unhealthy cells into the bloodstream. The test analyzed 13 different types of cancers and detected 79 percent of early-stage malignancies, with very few false positives. It also performed well in finding 58 percent of early-stage pancreatic cancers and 100 percent of early-stage liver cancers, both highly aggressive cancers that are rarely caught early (431).

Minimally invasive cancer screening, especially with blood-based tests, has the potential to transform how and when cancer is found. A growing body of evidence, including several of the studies highlighted here, shows that these tools can detect cancer signals with remarkable accuracy, even in people with no symptoms (433). But important challenges remain, such as unequal access, limited insurance coverage, lack of transparency about what markers the tests are detecting and what the findings might mean, and concerns about missing cancers, especially precancerous lesions or early-stage cancers, or unclear results (434–436). Continued research is essential to improving test performance, ensuring equity, and validating how well these tools work in everyday clinical settings so that their benefits reach all communities, with the ultimate goal to reduce cancer-related mortality.

Advances in Imaging

Imaging plays a critical role in the early detection of cancer by revealing tumors and abnormal tissue changes before symptoms appear. These technologies often guide diagnosis and treatment decisions. Advances in low-dose CT, MRI, and molecular imaging are now making it possible to detect cancer earlier, with greater precision and fewer harms. Although not recommended by USPSTF, whole body MRI—an established screening tool for children with cancer predisposition syndrome (e.g., Li-Fraumeni syndrome)—is also being used in adults to look for cancer (437). Increasingly, researchers are also integrating traditional imaging methods with AI and novel ways to visualize cancer cells to improve the accuracy of cancer detection and reduce the chances of missed diagnoses.

In a promising application, researchers are exploring how advanced MRI techniques might enable earlier detection of pancreatic cancer, one of the deadliest cancer types due to its typically late diagnosis. A recent study tested two specialized MRI methods in mice as well as in human pancreatic tissue (438). These imaging techniques were able to detect early warning signs of pancreatic cancer, called PanIN lesions, that are invisible on standard scans. This approach may offer health care teams a new way to identify pancreatic cancer before it progresses, offering hope for earlier intervention in a disease with extremely low survival rates.

Imaging is also improving how prostate cancer is diagnosed after elevated prostate-specific antigen (PSA) levels are detected. Traditionally, a biopsy is performed after a suspicious PSA result, but this invasive procedure often detects slow-growing cancers that would not have advanced or caused harm (439). New evidence supports using MRI after a positive PSA test to decide whether a biopsy is necessary. MRI improves visualization of suspicious prostate lesions, including cancers that require clinical intervention, and helps distinguish them from benign cancers that are less likely to pose a threat to a person's health (440). In a study of more than 13,000 men ages 50 to 60, MRI-guided screening led to fewer unnecessary biopsies and reduced low-risk cancer diagnoses by 57 percent, without missing the number of aggressive or incurable cancers detected (441). Another study found that 86 percent of men who had a negative MRI result completely avoided the need for a biopsy at a 3-year follow-up. MRI still detected cancers that required treatment (442). These findings support a shift in prostate cancer screening toward a more precise, MRI-guided approach that limits harm and avoids overdiagnosis without missing prostate cancer cases that require treatment.

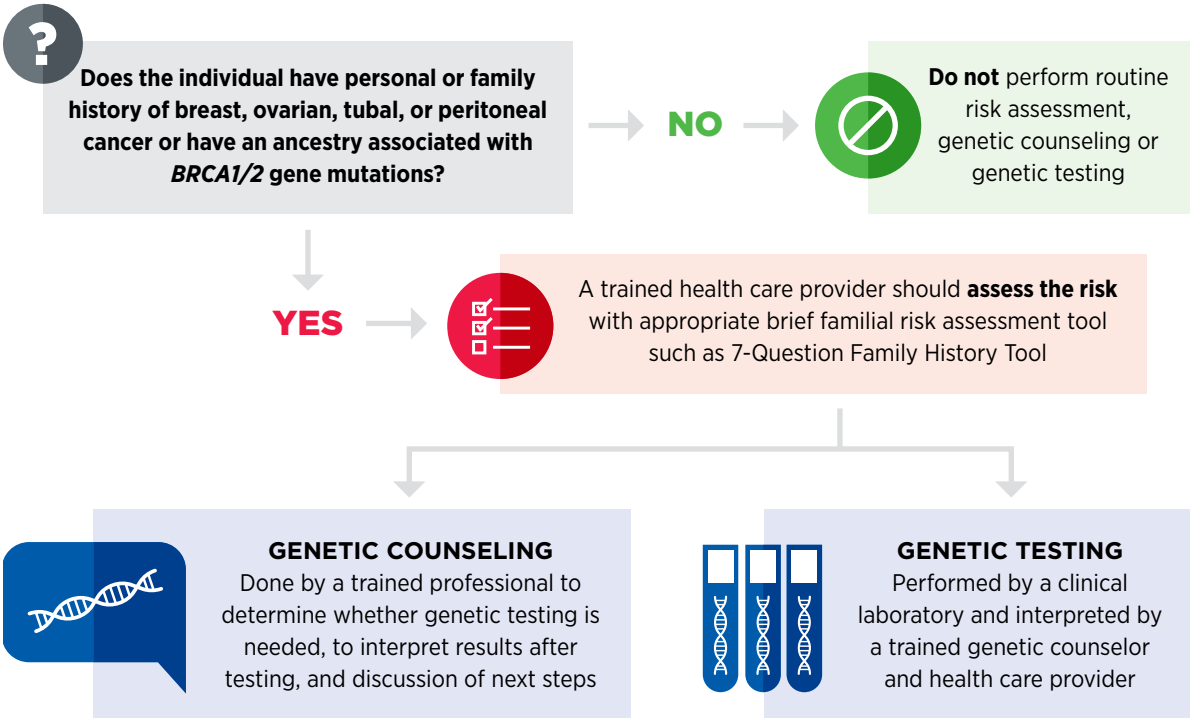
The advances discussed here highlight the expanding role of imaging in transforming early cancer detection. From identifying aggressive tumors to reducing invasive procedures, imaging innovations are helping to make cancer screening more accurate, more personalized, and less burdensome. With continued research and clinical validation, these tools could dramatically improve how we detect and ultimately treat cancer across many different types.

Genetic Insights Advancing Cancer Risk Reduction and Interception

Genetic testing examines DNA to identify changes that may influence cancer risk, diagnosis, or treatment. Germline testing, which looks for inherited genetic mutations (see **Genetic Alterations**, p. 34), is not a tool for detecting

FIGURE 14

USPSTF Recommendation for Breast Cancer Genetic Testing



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

cancer itself but plays a critical role in identifying individuals at elevated lifetime risk—particularly those with a strong family history of cancer (see **Sidebar 23**, p. 74). When a harmful mutation is found, patients can receive personalized care that may include genetic counseling, targeted screening, or preventive interventions like risk-reducing surgeries (see **Supplementary Table 2**, p. 264).

Germline testing differs from somatic testing, which analyzes tumors for mutations acquired during a person's lifetime. Somatic mutations are not inherited and help guide cancer treatment, prognosis, and monitoring. Both approaches are crucial but germline testing is uniquely positioned to shift cancer care from reactive to proactive and can also help family members plan their care accordingly if a close relative tests positive for a germline mutation that may place them at higher risk of developing cancer.

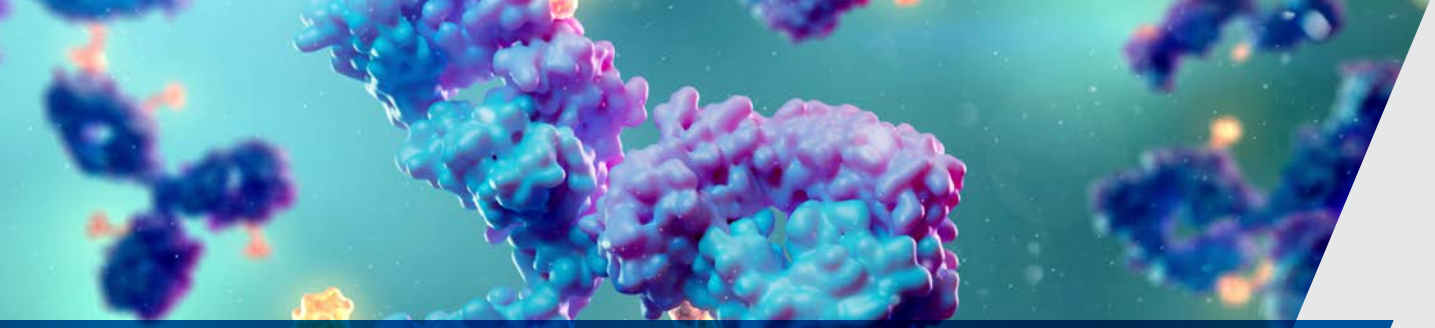
An increasing body of evidence shows that it is not always one mutation, but the combined small effects of many inherited genetic changes, that leads to cancer (443). A rapidly emerging tool within germline testing is the polygenic risk score (PRS), which quantifies the cumulative effect of dozens to hundreds of common inherited variants. PRS is now used in clinical settings to enhance breast cancer risk prediction and tailor screening strategies in women with mutations that almost always cause cancer (444). Furthermore, researchers are evaluating the effectiveness of PRS in determining the risk of other cancer types. Findings from a recent study showed that PRS improved selection of patients with prostate cancer who needed clinical intervention, as well as reducing unnecessary biopsies and overdiagnosis (445). Ongoing research is also investigating the role of environmental factors in increasing cancer risk and exploring whether incorporating environmental factors along with PRS will further refine the effectiveness of such scores (446,447).

Individuals with a family or personal history suggestive of inherited cancer syndromes should discuss genetic counseling and testing with their health care provider. Expert panels issue clinical guidelines to support this process. For example, USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer—or with ancestry linked to *BRCA1/2* mutations, such as those of Ashkenazi Jewish ancestry—using a validated risk tool. Those with positive results should be referred for genetic counseling and, if appropriate, genetic testing (see **Figure 14**, p. 86). These recommendations are currently being updated.

The understanding of genetic mutations associated with cancer-predisposing syndromes (see **Figure 6**, p. 36) is also enabling strategies, such as cancer interception (see **Figure 24**, p. 172), that can mitigate or altogether eliminate a person's chances of developing cancer. Researchers are developing preventive vaccines that aim to stop cancer from developing and that are particularly promising for individuals at high risk of developing cancer, such as those with inherited mutations or predisposition syndromes. One example of such an approach is an ongoing clinical study using a vaccine to prevent cancer development in individuals with Lynch syndrome, who have germline mutations in genes involved in DNA repair (448). Another example is an mRNA vaccine to prevent cancer in individuals who carry germline mutations in *BRCA1/2* genes and are at higher risk of developing cancers of the breast, ovary, pancreas, and prostate (449). Although in the early stages of clinical testing, these preventive cancer vaccines have the potential to revolutionize cancer surveillance, prevention, and care in people with germline mutations.

Germline mutations account for approximately 10 to 15 percent of all childhood cancers (450–452) and often confer a high lifetime cancer risk with early onset of disease. Identifying these mutations enables early surveillance and timely intervention. While historically few standardized surveillance protocols existed for these syndromes, the American Association for Cancer Research convened a 2016 workshop to develop consensus recommendations for early cancer detection in affected children (453). A follow-up workshop in 2023 expanded and updated these guidelines to reflect new evidence and include newly identified syndromes, while also exploring emerging surveillance technologies and potential prevention strategies for high-risk pediatric populations (454). Surveillance now begins at birth or during early childhood, depending on the syndrome, with imaging and blood tests prioritized over CT to reduce radiation exposure. These protocols aim to catch tumors early when cure rates exceed 90 percent, such as for Wilms tumor or hereditary retinoblastoma.

These advances underscore the expanding role of genetic testing in cancer prevention, not by detecting cancer itself but by identifying those most likely to develop it. As clinical guidelines evolve and tools like PRS mature, germline testing will continue to shift cancer care toward earlier, more personalized intervention—often before a single symptom appears.



Unifying Cancer Science and Medicine: A Continuum of Innovation for Impact

IN THIS SECTION, YOU WILL LEARN:

- Researchers are leveraging insights into the cellular and molecular mechanisms of cancer initiation and progression 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, 2024, to June 30, 2025, the US Food and Drug Administration (FDA) approved 20 new therapeutics for treating various cancer types, approved one new device for treating lung cancer, and expanded the use of eight previously approved anticancer therapeutics to treat additional cancer types.
- Among FDA approvals are a new molecularly targeted therapy against a novel target for patients with lung cancer and pancreatic cancer, a new targeted therapy for a specific type of brain tumor, and a new form of immunotherapy—T-cell receptor (TCR) T-cell therapy—for patients with a rare sarcoma.
- 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 2025**, p. 14, and **Supporting Cancer Patients and Survivors**, p. 177). This progress is attributable, in part, to the rapid advances in cancer treatment propelled by breakthroughs across the continuum of medical research.

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. 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 (see **Sidebar 6**, p. 31). 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 (see **Figure 5**, p. 32).

If a potential therapeutic target is identified, it takes many more years of preclinical research before a candidate therapeutic is developed and ready for testing in clinical

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

W39

trials (see **Sidebar 27**, p. 90). 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 a therapeutic can be approved by the US Food and Drug Administration (FDA) and used as part of routine patient care. Institutional review boards critically review and approve all clinical studies before they can begin. Clinical trials are 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.

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 treatment or standard treatment are called randomized clinical trials and are considered the most rigorous.

Participating in a clinical trial has several benefits. These include access to potentially more effective treatments with careful monitoring before they are widely available, an active involvement in making health care decisions, and a direct contribution to lifesaving cancer research (455).

Along with private sector–sponsored clinical trials, National Cancer Institute (NCI)–supported studies play a vital role in the development of novel anticancer treatments. Researchers estimate that over the past four decades, clinical trials funded by NCI contributed to 14 million additional years of life for cancer patients in the United States (68). Additionally, NCI-funded clinical research has been critical in advancing our knowledge in key areas such as treatment de-escalation (see **Minimizing the Use of Invasive Cancer Surgery**, p. 100), improving quality of life, and survivorship (see **Supporting Cancer Patients and Survivors**, p. 177) (456). Unfortunately, between 2008 and 2022, enrollment in federally funded cancer clinical trials remained flat while enrollment in private sector–sponsored trials doubled (457). While industry investment has accelerated the development of breakthrough cancer treatments, these data highlight the growing reliance on the private sector and concerning underinvestment in publicly sponsored research (see **Investing in Research to Achieve a Healthier Future**, p. 209).

Clinical trials testing 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 anticancer efficacy of a therapeutic. However, because of rapid progress in clinical trial design and conduct, phase I trials are increasingly incorporating a preliminary evaluation of efficacy (458). 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 (459).

Phase II studies 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 standard of care; when successful, the results of these trials have traditionally been used by FDA to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy 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.

One in six patients in phase II cancer clinical trials receive a treatment that is eventually approved by the US Food and Drug Administration. The **proportion is higher for patients participating in biomarker-driven or immunotherapy trials**.

Source: (460).

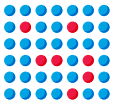
W40

SIDEBAR 27

Therapeutic Development

Target validation

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

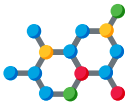


Drug screening

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

Lead identification

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



Lead optimization

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

Preclinical testing

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 candidate(s).

Investigational new drug

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

Source: (177).

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 frequency, and therapies designed to target those changes are actively being evaluated in clinical trials. Identifying and implementing more efficient clinical development strategies are areas of extensive investigation.

Innovations in Cancer Clinical Trials

Technological innovations in genomics, as well as in fields such as epigenomics, transcriptomics, proteomics, metabolomics, immunomics, and microbiome research, are giving researchers a more complete understanding of what drives tumor growth and the molecular changes that should be prioritized as targets for new therapeutics (see **Cancer Development: Integrating Knowledge to Advance Precision Medicine**, p. 46). This growing knowledge has revealed the heterogeneous cellular and molecular landscape of advanced and metastatic cancers. Characterizing tumors at the cellular and molecular levels is also helping clinical researchers identify subsets of patients who are more likely to respond to investigational new therapies.

Consequently, over the past decade, clinical cancer research has undergone significant evolution from traditional drug-centric, tissue-specific trials to tissue-specific, genomically driven trials to most recently biomarker-driven clinical trials based on specific genetic or molecular features of a cancer, regardless of where in the body the cancer started (see **Sidebar 28**, p. 91). Biomarker-driven clinical studies,

SIDEBAR 28

A New Age of Cancer Clinical Trials

Recent advances in our understanding of genetic, epigenetic, immune, and other biological drivers of cancer have led to novel ways of designing and conducting clinical trials. Among the new concepts and designs for clinical trials that have emerged in recent years are the following (462):

Master protocols

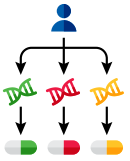
Also known as **main protocols**, refer to an overarching trial design that can answer multiple clinical questions. By allowing the evaluation of multiple new agents simultaneously and by matching the right therapeutics with the right patients earlier, master protocols reduce the number of patients who 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 (463).

BASKET TRIALS

Allow researchers to test one anticancer therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original cancer.
Example: NCI-MATCH clinical trial.

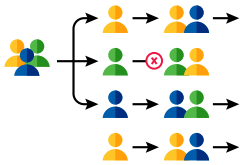
UMBRELLA TRIALS

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



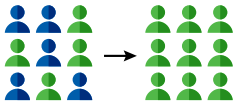
PLATFORM TRIALS

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.



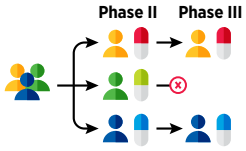
Adaptive trial designs

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 (464).



Seamless trial 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 allows research questions to be answered more quickly or with fewer patients. Seamless trial designs can allow FDA to approve promising new therapies without waiting for traditional, large phase III trials, by enabling earlier access to robust efficacy and safety data within a single, continuous study.
Example: CodeBreaK 100 phase I/II trial (465).



N of 1 clinical trial designs

Patient-centered approaches that provide a unique therapy to each patient based on their individual tumor profiles.
Example: I-PREDICT study (466).

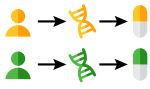
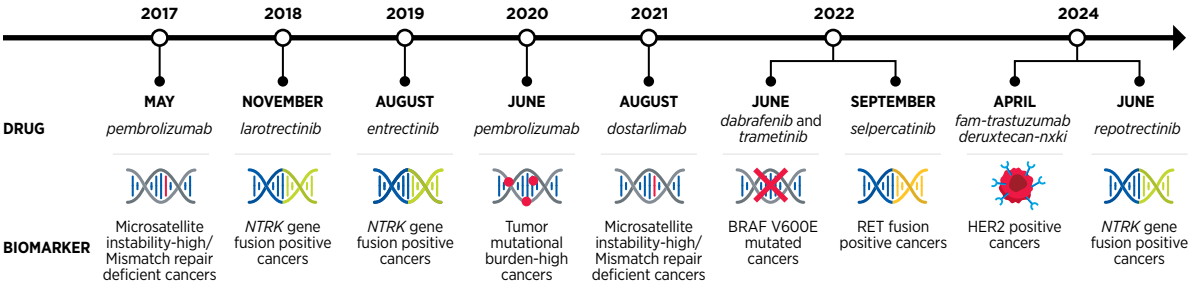


FIGURE 15

Timeline of Tissue-agnostic FDA Approvals of Cancer Treatments



A watershed moment in cancer medicine was the May 2017 US Food and Drug Administration (FDA) approval of the immunotherapy medication 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 microsatellite instability-high and 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. Since then, there have been seven more site-agnostic approvals. In addition, the 2021 FDA approval of belzutifan for cancers of the kidney, brain, and pancreas associated with Von Hippel–Lindau, which is an inherited disorder, and the 2022 FDA approval of pemigatinib for myeloid/lymphoid neoplasms, a small group of blood cancers, can be viewed as site-agnostic.

Adapted from (467).

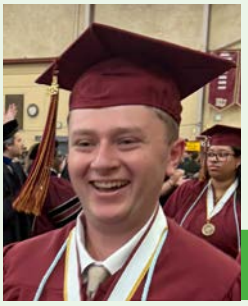
which evaluate therapies in patients regardless of the site of their cancer's origin, are more often being used to support tissue-agnostic regulatory approvals for all tumors that have the targeted biomarker. As of June 30, 2025, nine therapeutics have received tissue-agnostic approvals from FDA for treating patients with solid tumors that have specific genetic alterations (see **Figure 15**, p. 92).

According to a recent analysis of nearly 300,000 tumor samples, more than 20 percent of tumors harbored at least one molecular alteration that is associated with tissue-agnostic treatment approval. Unfortunately, electronic health records of clinical outcomes indicated a poor uptake of treatments for tissue-agnostic indications; for example, less than 40 percent of patients with *NTRK* fusions received a corresponding targeted treatment (461).

Researchers continue to work on refining and reshaping aspects of clinical research to make trials more patient-focused (462). There is an urgent call for a paradigm shift from traditional trial designs, in which patients are identified to fit an investigational therapy, to more patient-centric approaches, in which novel therapeutics are identified for each patient based on the unique features of their cancers (468). By harnessing novel technologies, such as advanced DNA and RNA sequencing, researchers aim to develop patient-centric clinical trial designs that deliver therapies targeting genetic alterations, regardless of cancer site, offering novel treatment options for patients with shared molecular features, including those with rare cancers (469).

A key feature of patient-centric trials is the ongoing monitoring of tumor characteristics throughout clinical care, rather than relying on a single assessment prior to the start of the study, as has been traditionally done. Using novel methodologies, such as liquid biopsy (see **Envisioning the Future of Cancer Science and Medicine**, p. 194) and digital imaging, researchers are now able to identify dynamic changes in the cancer cells, the tumor microenvironment, and the patient's immune system that reflect their cancer's evolution (see **Understanding the Path to Cancer Development**, p. 29).

Thank you does not seem like enough! My outcome would have very likely been different without cancer research and clinical trials!



"I am in a survivor program. I was diagnosed 10 years ago with ALL and did not respond to the standard of care treatments. I was enrolled in a study, had CAR T-cell therapy which got me to a point where I could have a bone marrow transplant... I just now graduated in May [2025] from Kutztown University, and I will start in my profession as a teacher this September."

Luke Theodosiades

Scan to read Luke's story in *AACR Cancer Progress Report 2016*

Collecting such multidimensional data over time enables researchers to adapt therapeutic interventions, treatment dosages, or other aspects of the clinical trial protocol to more effectively manage tumor evolution and emerging resistance mechanisms. For example, researchers may decide, based on emerging molecular alterations, that combination therapy targeting multiple cancer drivers may be more effective.

In looking to the future, the design and conduct of clinical cancer research needs 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. 214) (470).

While many precision therapeutics are evaluated in late-stage cancer, once standard treatments have failed, 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.

Another shortcoming that has restricted the scope of current clinical research is underutilization of the 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, patient reported outcomes, and insights from patient advocacy communities is pivotal to driving meaningful progress and transforming the future of cancer clinical trials (468).

Harnessing artificial intelligence (AI) and machine learning trained on diverse datasets can further improve clinical research. AI tools are 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 work; create "digital twins" or virtual control groups using past patient data—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 Science and Medicine**, p. 194) (471–474). However, there are limitations to the current use of AI, including lack of data diversity and proper regulatory oversight, that must be overcome before these tools can become 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 29**, p. 94). Based on recent estimates, only 7 percent of cancer patients nationwide participate in treatment trials (475). Low participation in clinical trials means that many trials fail to enroll enough patients to draw meaningful conclusions about the effectiveness of the investigational therapeutic. Lack of diversity in clinical studies means that the trial participant population does not match the actual national demographics of the cancer burden under study (476). Diversity of participants is critical because the efficacy and safety of an intervention may differ among populations, for example, among different ancestral groups or between men and women. Underrepresentation in clinical trials compromises the generalizability of the trial findings to the real-world patient population.

Understanding and eliminating barriers to clinical trial participation is vital if we are to accelerate the pace of progress against cancer for all patients. Numerous studies have

SIDEBAR 29

Disparities in 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. Despite this knowledge, several segments of the US population are underrepresented in clinical trials attributable to multifactorial barriers to participation. Examples of these disparities include the following:

Only 1% and 8%	The US Food and Drug Administration (FDA) approval of the novel therapeutic zolbetuximab-clzb for patients with gastric or gastroesophageal junction cancer was based on a clinical trial in which only 1 percent and 8 percent of participants were Black and Hispanic, respectively (477). This is in stark contrast to their proportion among new gastric cancer cases in the United States, for which Black and Hispanic individuals represent 16 percent and 17 percent, respectively (478).
Only 1% and 16%	FDA approval of inavolisib for certain patients with breast cancer was based on a clinical trial in which only 1 percent of participants were Black and only 16 percent of participants were 65 or older (479). Black individuals accounted for 15 percent of US breast cancer deaths and patients 65 and older accounted for 67 percent of US breast cancer deaths in 2023 (478).
86% less likely	Counties with higher social vulnerability—such as poverty, lack of access to transportation, or crowded housing—have 18 more prostate cancer deaths per 100,000 people compared to less vulnerable counties. However, these same counties are 86 percent less likely to have any prostate cancer clinical trials available (480).
86% vs. 44%	A recent analysis of 6,710 clinical trials showed that 70 percent of US counties had no active cancer trials. The gap was wider in rural areas—86 percent of nonmetropolitan counties lacked trials, compared to 44 percent of metropolitan counties (481).
60% less likely	A retrospective analysis of clinical trial participation among children and adolescents with blood cancer showed that Black patients were 60 percent less likely than White patients to enroll in a trial (482).
FEWER clinical trials available	Analysis of 1,561 gynecologic cancer clinical trials found that US states with higher social vulnerability as well as those with mostly minoritized populations (meaning less than 50 percent non-Hispanic White residents) had fewer clinical trials available (483).
More than 70%	Analysis of phase III clinical trials from the past decade that were evaluating interventions for acute myeloid leukemia (AML) showed that more than 70 percent of participants were less than 65 years old (484), even though the incidence of AML is highest among those aged 65 years or older.

investigated the existing barriers that limit participation of racial and ethnic minority groups and other medically underserved populations in cancer clinical trials. These studies have identified a range of factors, such as lack of awareness of clinical trials, financial challenges, limited health literacy, inadequate or complete lack of insurance, medical distrust, implicit biases among health care providers, lack of trial availability, and narrow eligibility criteria, among others (485). These barriers operate at the individual, systemic, and societal levels (486).

As discussed in detail in *AACR Cancer Disparities Progress Report 2024* (12), increased knowledge of the barriers to

In the United States, a higher proportion **(nearly 20%) of pediatric and adolescent patients with cancer, compared to adults, participate in clinical trials**. Enrollment of pediatric patients from racial and ethnic minority groups is also higher than that of adult patients.

Sources: (487,488).

W41

clinical trial accrual is helping researchers, regulators, and policymakers design and implement evidence-based adaptations that can improve access to clinical research. Interventions aimed at addressing social drivers of health (see **Figure 3**, p. 22), 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 being evaluated. Researchers are also leveraging AI to increase clinical trial participation and diversity by improving patient matching, identifying underserved populations, and streamlining recruitment processes. Additionally, a 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.

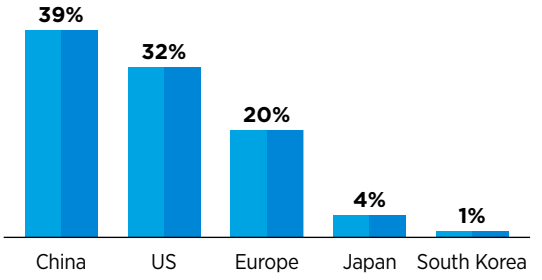
US lawmakers and FDA have been working on legislation and guidelines intended to increase the diversity of clinical trial participants (12). These include a diversity action plan that would require researchers and funders of clinical trials to submit concrete goals and needed steps for enrolling specific demographic groups in pivotal studies that are used by FDA to make regulatory decisions on new drugs (489). However, recent actions from the Administration are jeopardizing progress in this critical area of cancer medicine. Reductions in FDA staffing and funding, along with the elimination of clinical trial diversity initiatives, threaten to delay innovations and treatments that are essential not only for advancing care but also for ensuring all patients have equitable access to lifesaving therapies.

COVID-19, despite its adverse effects on all aspects of cancer research and patient care, enabled researchers to decentralize certain aspects of clinical trials so that lifesaving therapeutics could be brought quickly to as many patients as possible (490). 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 (see **Increasing Access to and Decentralizing Trials**, p. 216). It is, therefore, not surprising that the number of decentralized trials rose sharply beginning in 2020, following only modest growth from 1998 to 2019 (491).

Emerging data indicate that patient-centric approaches can improve outcomes. As an example, a supportive care clinical trial that involved partnerships between leading academic centers and community health centers reduced early deaths in patients with acute promyelocytic leukemia (APL), from an expected 30 percent to just 3 percent, across all care settings (492). Patients at community centers were treated locally using a consensus treatment plan developed through collaboration between the community oncologist and one of seven APL experts available from six lead academic centers.

Ongoing research must continue to evaluate the impact of decentralized approaches on advancing clinical research and improving patient outcomes (493). A decentralized infrastructure may also improve the conduct of clinical trials globally. Unfortunately, despite investments of over $80 billion annually, less than 5 percent of cancer patients globally participate in clinical trials (494). Low participation is particularly pronounced in low- and middle-income countries (LMICs), where access to trials is limited (495). In fact, nearly 90 percent of all clinical trials are conducted in high-income regions and countries, including the United States, China, Japan, and Europe (494). While Africa comprises nearly 15 percent of the world's population and carries 25 percent of the global burden of the disease, less than 2 percent of all cancer clinical trials are conducted there (494). In addition, based on a recent analysis of 50,073 oncology trials listed on the ClinicalTrials.gov website between January 2005 and March 2023, only 666 trials (1.3 percent) included study sites in Middle Eastern and North African countries (496).

Geographic Distribution of Industry-sponsored Phase I–III Cancer Clinical Trials in 2024*



* Based on company headquarters location.

Source: (497).

W42

Expanding global access to cancer clinical trials must become a strategic priority for all stakeholders committed to accelerating breakthroughs in cancer care. Notably, multiregional clinical trials that enroll patients from multiple countries are becoming more common, especially for therapeutics developed by major multinational biopharmaceutical companies. This approach to clinical trials may offer many benefits, such as accelerating therapeutic development, including more diverse populations, and helping ensure new treatments work safely and effectively for people around the world (498).

Together with diversity action plans to improve representation of different racial, ethnic, age, and sex groups in trials, these global efforts can promote diversity in clinical research (see **Increasing Access to and Decentralizing Trials**, p. 216). By carefully planning trial locations, for example, enrolling from countries in South and Central America, the Middle East, and Africa, where many underserved US patients have ancestral origins, researchers can build stronger, more inclusive studies that better represent the populations likely to use the treatments.

In this regard, in September 2024, the World Health Organization released new guidance to improve the design, conduct, and oversight of clinical trials, aiming to strengthen country-led research ecosystems, enhance trial quality and coordination, and ensure faster, more equitable access to safe and effective health interventions worldwide (499).

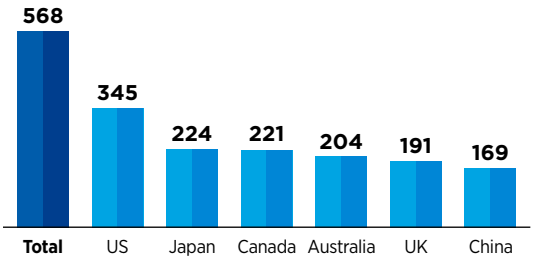
Progress Across the Clinical Cancer Care Continuum

Research discoveries made as a result of innovative cancer science are continually being translated into new medical products for cancer prevention, early detection, diagnosis, and treatment. The United States has significantly benefited from its role as the world's largest funder of medical research. Recent data show that it leads worldwide in the introduction of new cancer therapies and is most often the first to bring these treatments to the clinic (69).

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 (see **Figure 5**, p. 32) 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 16**, p. 97). 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. Additionally, researchers are continually evaluating new ways to refine the use of surgery, radiotherapy, and chemotherapeutics to improve survival and quality of life for patients.

Between 1990 and 2022, **568 new cancer drugs** were launched worldwide.



Source: (69).

W43

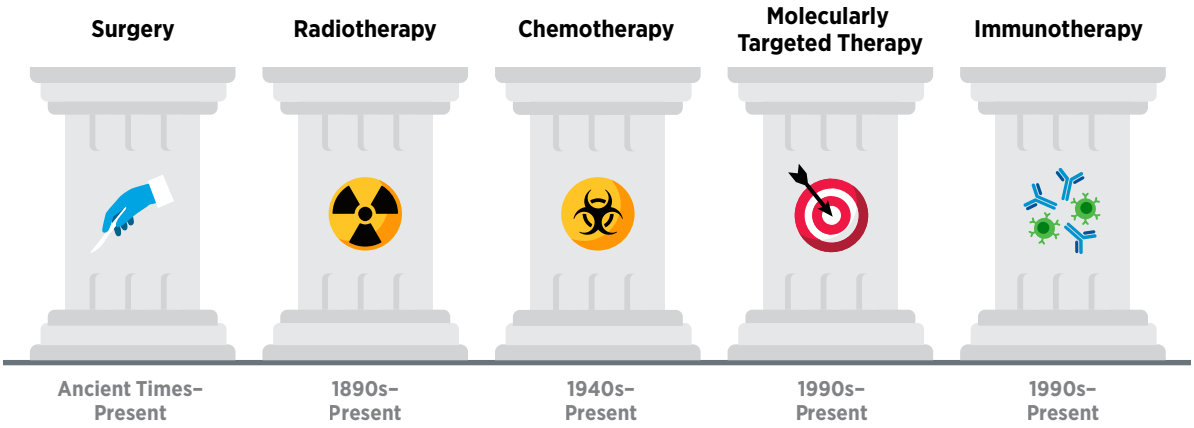
Prostate cancer offers a clear example of advances in treatment refinement. Most tumors grow slowly, and the significant morbidity and costs associated with diagnosing and treating these tumors may outweigh the benefit for many patients. Treatments such as surgery can have lasting side effects, and many men with slow-growing prostate cancer may never experience problems during their lifetime. Research has shown that careful observation of disease in patients with nonaggressive prostate cancer (also referred to as watchful waiting or active monitoring) is a safe alternative to receiving immediate surgery or radiotherapy (500,501). These findings are hopeful for patients who opt for active monitoring to avoid treatment-related adverse effects, such as sexual and incontinence problems. Recent data also indicate that among patients with nonaggressive prostate cancer the use of active monitoring has been increasing, particularly within certain sociodemographic groups, while surgical interventions are declining (502–504).

Active monitoring has also proven to be a safe approach for some patients with thyroid cancer and those with an early, non-invasive form of breast cancer, called ductal carcinoma *in situ* (505,506).

The following sections focus on the recent advances across the five pillars of cancer treatment, in particular, the 20 new anticancer therapeutics approved by FDA in the 12 months spanning this report, July 1, 2024, to June 30, 2025 (see **Table 6**, p. 98, and **Supplementary Table 3**, p. 265). During the same timeframe, FDA expanded the use of eight previously approved anticancer therapeutics and one medical device for treating additional types of cancer. Furthermore, FDA expanded the use of several previously approved therapeutics to include treatment at different timepoints during the course of clinical care or treatment of a different subtype of the same cancer. Comprehensive information

FIGURE 16

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 (507). In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar (508). The foundations for the third treatment pillar—chemotherapy—were established in the early 1940s, with the use of a derivative of nitrogen mustard to treat lymphoma (509). These three pillars—surgery, radiotherapy, and chemotherapy—continue to be critical components of cancer treatment. Introduction of the first molecularly targeted therapeutics in the late 1990s led to the establishment of the fourth pillar, molecularly targeted therapy (510). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (511). 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.

on all anticancer therapeutic approvals can be found on FDA's website (512). 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 **Supporting Cancer Patients and Survivors**, p. 177). 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 in cancer treatment are driven largely by socioeconomic and structural factors, such as lack of health insurance or access to health care facilities, as well as high costs of cancer care (see **Sidebar 30**, p. 99). There are also stark differences in the cost and accessibility of cancer treatments around the world, with major disparities between high-income and low-income countries (513). On the basis of 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 (514).

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 (12). As one example, some studies have found no racial or ethnic disparities in cancer outcomes among patients who are treated at a single-payer system, such as the US Department of Veterans Affairs' Veterans Health Administration, the nation's largest integrated health care system (515).

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 reduce cancer disparities, leading to improved outcomes for patients (516–518). Therefore, it is imperative that all stakeholders in public health work together to ensure equitable access to quality cancer treatments.

Educating health care providers about the approval processes for relevant therapeutics is critical if they are to adequately

TABLE 6

Newly FDA-approved Anticancer Agents (July 1, 2024–June 30, 2025)

Type of Treatment	Generic Name	Trade Name	What It Is	Approved For
MOLECULARLY TARGETED THERAPY	▶ avutometinib + defactinib	Avmapki + Fakzynja	Cell-signaling inhibitor	Certain type of ovarian cancer
	belzutifan	Welireg	Gene transcription modifier	Pheochromocytoma or paraganglioma†
	cabozantinib	Cabometyx	Angiogenesis inhibitor	Certain types of pancreatic and extra-pancreatic neuroendocrine tumors†
	▶ datopotamab deruxtecan-dlnk	Datroway	Cell-signaling inhibitor	Certain types of breast and lung cancers
	▶ denileukin diftitox-cxdl	Lymphir	Cell-lysis mediator	Certain type of lymphoma
	▶ ensartinib	Ensacove	Cell-signaling inhibitor	Certain type of lung cancer
	▶ inavolisib* + palbociclib + fulvestrant	Itovebi	Cell-signaling inhibitor	Certain type of breast cancer
	▶ lazertinib + amivantamab-vmjw	Lazcluze + Rybrevant	Cell-signaling inhibitor	Certain type of lung cancer
	▶ mirdametinib	Gomekli	Cell-signaling inhibitor	Plexiform neurofibromas
	▶ revumenib	Revuforj	Gene transcription modifier	Certain types of leukemia
	sotorasib* + panitumumab	Lumakras + Vectibix	Cell-signaling inhibitor	Certain type of colorectal cancer†
	▶ taletrectinib	Ibtrozi	Cell-signaling inhibitor	Certain type of lung cancer
	▶ telisotuzumab vedotin-tllv*	Emrelis	Cell-signaling inhibitor	Certain type of lung cancer
	▶ vimseltinib	Romvimza	Cell-signaling inhibitor	Tenosynovial giant cell tumor
	▶ vorasidenib	Voranigo	Epigenome-modifying agent	Certain types of brain tumor
	▶ zanidatamab-hrii*	Ziihera	Cell-signaling inhibitor	Biliary tract cancer
	▶ zenocutuzumab-zbco	Bizengri	Cell-signaling inhibitor	Certain types of lung and pancreatic cancers
IMMUNOTHERAPY	▶ afamitresgene autoleucel	Tecelra	TCR T-cell therapy	Synovial sarcoma
	▶ cosibelimab-ipdl	Unloxcyt	Immune checkpoint inhibitor	Cutaneous squamous cell carcinoma
	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of bladder cancer†
	▶ obecabtagene autoleucel	Aucatzyl	CAR T-cell therapy	Certain type of leukemia
	pembrolizumab	Keytruda	Immune checkpoint inhibitor	Pleural mesothelioma†
	▶ penpulimab-kcqx	–	Immune checkpoint inhibitor	Nasopharyngeal carcinoma
	retifanlimab-dlwr	Zynyz	Immune checkpoint inhibitor	Certain type of anal cancer†
	tafasitamab-cxix	Monjuvi	Cell-lysis mediator	Certain type of lymphoma†
	▶ zolbetuximab-clzb*	Vyloy	Cell-lysis mediator	Gastric or gastroesophageal junction cancers
DEVICE	Optune Lua		Tumor treating fields device	Certain type of lung cancer†

▶ Denotes newly approved anticancer agents.

CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; TCR, T-cell receptor.

* Approved with a new companion diagnostic test.

† Expanded approval for use in new cancer type.

SIDEBAR 30

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 systemic inequities, and are less likely to receive recommended treatments. Examples of these disparities include the following:

35% more likely	Breast-conserving therapy, combining lumpectomy and radiation, provides outcomes equivalent to mastectomy for early-stage breast cancer, yet disparities persist—with Native Hawaiian or Other Pacific Islander women 35 percent more likely than White women to refuse recommended radiation therapy (520).
12% less likely	In a study of over 100,000 patients with early-stage triple-negative breast cancer—an aggressive form of the disease—Black patients were 12 percent less likely than non-Hispanic White patients to receive neoadjuvant chemotherapy, a treatment given before surgery that can improve outcomes (521).
LESS likely	Pancreatic cancer patients with lower socioeconomic status, and those who are uninsured, are less likely to receive surgery or chemotherapy (522).
59% and 19% less likely	In a study of more than 3,000 patients with metastatic HER2-positive breast cancer, those who were 71 or older and Black were 59 percent and 19 percent less likely, respectively, to receive HER2-targeted therapy, despite its strong association with significantly improved survival (26).
SIGNIFICANTLY less likely	Black women with metastatic breast cancer were significantly less likely than White women to receive PI3K-targeted therapy, even though both groups had similar rates of the genetic changes these drugs are meant to treat, highlighting a serious treatment gap that may help explain worse outcomes for Black patients (523).
50% less likely	Compared to cisgender patients with breast cancer, transgender and gender diverse patients were 50 percent less likely to receive endocrine therapy for hormone receptor–positive disease and had inferior survival (524).

advise patients about the risks and benefits associated with these treatments. Unfortunately, according to a recent national survey of physicians including oncologists, only 41 percent of respondents reported moderate or better understanding of FDA's drug approval process (519).

Advances in Cancer Treatment With Surgery

For centuries, surgery was the only pillar of cancer treatment (see **Figure 16**, p. 97). Today, it remains the foundation of curative treatment for many patients. Surgery is used in several ways during the care of a patient with cancer (see **Sidebar 31**, p. 100).

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 32**, p. 101). 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 (525). Researchers are

SIDEBAR 31

Using Surgery for Cancer Treatment

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

Diagnose cancer

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

Stage cancer

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

Cure cancer

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

Debulk cancer

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

Ease problems caused by cancer

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

Surgery for patients with cancer can be open or minimally invasive.

OPEN SURGERY

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

MINIMALLY INVASIVE SURGERY

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

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

continuously innovating new and improved strategies to maximize the benefits and minimize harm from surgery for cancer patients.

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 improving, long-term outcomes (526–529). 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 report, the use of neoadjuvant therapy has significantly increased since 2010, particularly for breast, pancreatic, and bladder cancers (530).

Emerging data suggest that certain patients who have achieved a complete response, that is, those who have no detectable cancer, after neoadjuvant treatments (see **Sidebar 32**, p. 101), can skip surgery without compromising outcomes. As one example, a recent study conducted in the Netherlands suggests that some patients with locally advanced esophageal cancer may safely avoid surgery if they respond well to neoadjuvant chemotherapy and radiotherapy (531). In the clinical trial, patients who showed no signs of cancer after neoadjuvant treatment were either closely monitored or underwent standard surgery. The study found that survival outcomes were similar in both groups, indicating that active monitoring may be a safe alternative to immediate surgery for selected patients.

SIDEBAR 32

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 radiation or chemotherapy is called *pathological 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.

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.

Treatment de-escalation

Effort to reduce the intensity of treatment without sacrificing efficacy.

Another new clinical trial showed that some women with certain types of invasive breast cancer may be able to safely avoid surgery after responding well to neoadjuvant systemic therapy (532). In this trial, women who showed no detectable cancer after neoadjuvant treatment were treated with radiation alone instead of surgery. After 5 years of follow-up, none of these patients had cancer recurrence in the treated breast, and all remained cancer-free.

One area of increasing 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 (see **Releasing the Brakes on the Immune System**, p. 128) (533).

Although these results are promising, more research is needed before such approaches can become standard clinical practice. Additionally, there is an urgent need to streamline research efforts, as a recent review of the global landscape of surgical de-escalation trials in breast cancer revealed significant duplication in ongoing studies (534).

Lymph node dissection is another area of cancer surgery in which de-escalation is becoming increasingly common. This procedure 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 (see **Circulatory and Immune Systems**, p. 41). Lymph node dissection is routinely performed in patients with solid tumors such as breast, colorectal, gastric, and 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 dissection carries a higher risk of complications.

For example, in breast cancer, axillary lymph node dissection (ALND)—an extended procedure historically performed when 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. Recent studies suggest that ALND offers no survival benefit over regional or sentinel lymph node biopsy (SLNB) and can be safely omitted in certain breast cancer patients, including those with small tumors and normal lymph nodes on imaging or those who respond well to neoadjuvant chemotherapy (535,536).

A clinical study in patients with bladder cancer has shown similar results (537). Some patients with muscle-invasive bladder cancer may have cancer cells in the lymph nodes near the bladder at the time of diagnosis. Despite limited research comparing local lymph node dissections to extended lymph node dissection, the more extensive surgery has become the standard of care. The study, which included nearly 600 patients with muscle-invasive bladder cancer, found that extended lymph node removal during bladder surgery did not improve survival compared to limited node surgery but was linked to a higher risk of serious side effects and death within 90 days (537).

A study of over 1.2 million **women with gynecologic cancers** found that the use of traditional surgery declined while **minimally invasive procedures**, regional lymph node dissection, and fertility-sparing approaches **increased**, from 2000 to 2020.

Source: (541).

W44

Researchers are also evaluating whether less invasive procedures including robotic surgeries could replace traditional surgery for certain patients. For example, 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. In a recent study that compared thermal ablation to surgical removal for patients with small colorectal tumors that had spread to the liver found that patients who received thermal ablation had similar survival rates compared to those who had surgery (538). Importantly, thermal ablation caused far fewer side effects and serious complications. Nonsurgical management with radiation-based ablative therapy was also shown to be an alternative option for localized pancreatic cancers, especially among patients for whom surgery is risky or could greatly worsen quality of life (539). Additionally, robotic surgery may offer important advantages for certain patients, for example, those with middle or low rectal cancer, as it was associated with fewer cancer recurrences and better outcomes after 3 years compared to laparoscopic surgery (540).

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 (see **Figure 16**, p. 97). Radiotherapy plays a central role in the management of cancer and works primarily by damaging DNA, leading to cancer cell death.

AS CANCER CASES CONTINUE TO RISE GLOBALLY, EXPERTS PREDICT THAT BY 2050, THE NEED FOR **TRAINED RADIOTHERAPY PROFESSIONALS** WILL GROW BY **MORE THAN 60%**

Source: (542).

W45

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 (542). Unfortunately, there are significant disparities 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 (542). 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 (542).

There are many types of and uses for radiotherapy (see **Sidebar 33**, p. 104). However, it is important to note that radiotherapy may also have harmful side effects, partly because of the radiation-induced damage to healthy cells surrounding the tumor tissue (543). 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 harms.

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 (544,545).

As one example, a major clinical trial led by the Children's Oncology Group found that some patients with Wilms tumor, the most common type of kidney cancer in children, can safely skip radiation therapy, helping to reduce its long-term adverse effects (546). Traditionally, the treatment for patients with stage IV Wilms tumor that has spread to the lungs has been chemotherapy and surgery, followed by radiation therapy to the lungs. Data from the trial suggest that nearly half of children with advanced Wilms tumor can avoid lung radiation if they respond well to initial chemotherapy (546). Children whose lung nodules disappeared after 6 weeks of standard chemotherapy continued treatment without radiation and had a 4-year survival rate of over 96 percent, which was similar to the rate in those who received radiation. Omission of radiation may help reduce serious long-term side effects, such as heart and lung damage or future cancers (see **Sidebar 48**, p. 179).

The new findings mark an important step toward customizing treatment to preserve survival while maintaining quality of life.

For women with early-stage breast cancer, surgery followed by radiotherapy has 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 that 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 (547–549). In addition, a 30-year follow-up study found that radiotherapy after breast-conserving surgery did not improve overall survival for some patients with early-stage breast cancer, suggesting that radiation may be safely omitted in certain patients (550).

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) and three-dimensional conformal radiation therapy (3D-CRT) (see **Sidebar 33**, p. 104) in non–small cell lung cancer (NSCLC) found IMRT was safer for patients (551). Over 5 years of follow-up, both treatment groups had similar survival rates and risk of developing new cancers. However, IMRT exposed the heart to less radiation than 3D-CRT and caused fewer serious cases of lung inflammation.

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 compared 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. As one example, SBRT was shown to be a safe, convenient, and effective treatment option for certain patients with prostate cancer, and allowed men to complete their treatment in a much shorter time—five sessions compared to a minimum of 20 that is used traditionally—without compromising outcomes (552).

Historically, the main use of radiotherapy in the treatment of patients with metastatic cancer has been to reduce or control symptoms of disease. However, recent studies have shown that radiotherapy targeted to the initial cancer site from which tumors have metastasized can improve survival for patients who have metastatic tumors at a limited number of sites, referred to as oligometastatic tumors (553). Moreover, studies have shown that stereotactic radiotherapy targeted to oligometastatic tumors can reduce the chances of disease progression and increase survival for patients who have solid tumors, such as prostate, lung, or gynecologic cancers (554–557).

SIDEBAR 33

Using Radiation in Cancer Treatment

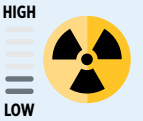
Ionizing radiation has two major applications in cancer care:

Treatment of cancer

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

Detection of cancer

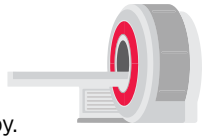
Radiology largely uses low-energy radiation to image tissues for diagnosing the disease.



Types of Radiotherapy

EXTERNAL BEAM RADIOTHERAPY

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



There are several types of external beam radiotherapy:

- **Conventional external beam radiation therapy** delivers a high-energy X-ray beam from one or more directions and is primarily used when high precision is not required.
- **Three-dimensional conformal radiotherapy (3DCRT)** delivers high-energy X-rays via multiple beams that, with the help of computed tomography and/or magnetic resonance imaging, enable more precise planning to best target the shape and size of the tumor.
- **Intensity-modulated radiotherapy (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 electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures, or to the tumor cavity immediately after cancer removal.
- **Stereotactic radiotherapy** delivers radiation to very well-defined smaller tumors, typically using 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, to the tumor with a dose distribution that better spares the exposure of surrounding tissue, because these particles deposit most of their energy in the target. Although of great interest, proton facilities are much more expensive than traditional facilities, and the overall benefit to patients remains to be defined.

BRACHYTHERAPY

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

RADIOISOTOPE THERAPY

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

Uses of Radiotherapy

CURATIVE RADIOTHERAPY

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

NEOADJUVANT RADIOTHERAPY

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

ADJUVANT RADIOTHERAPY

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

PALLIATIVE RADIOTHERAPY

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

SALVAGE RADIOTHERAPY

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

Theragnostics, or **theranostics**, 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, labeled with more potent radioactive compounds, are 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 these radiopharmaceuticals in additional cancer types. For example, a recent clinical study found that **Lutetium Lu 177 dotatate may help extend survival in patients with difficult-to-treat brain tumors known as meningiomas**.

Source: (565).

W46

Another recent advance in radiotherapy is the emergence of hypofractionated radiotherapy, whereby patients receive fewer but higher doses of radiotherapy compared to the traditional regimen (558). Patients who receive hypofractionated radiotherapy complete their radiation over a shorter period and in fewer treatment sessions. In a recent review, researchers indicate that this approach is just as effective as traditional, longer radiation courses for treating breast cancer, while also offering benefits like fewer side effects, better cosmetic results, improved quality of life, and greater convenience for patients (559). Despite established benefits for patients, hypofractionated radiotherapy is underused and there are disparities in uptake in the United States (560).

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. 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 (177,372,561), and many more are at various stage of preclinical and clinical testing (see **Radiopharmaceutical Therapy**, p. 207) (1,562–564).

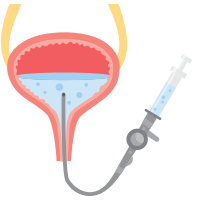
Molecularly targeted radiotherapeutics hold great promise for transforming cancer treatment, although challenges such as regulatory hurdles and complex manufacturing remain to be addressed. Additionally, access to these treatments has mostly been limited to high-income countries, as challenges like limited funding, shortages in sophisticated facilities for delivery, and insufficient trained medical personnel continue to hinder broader global use (542).

Ongoing research in theranostics 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. A recent analysis found that more than 60 novel radiotherapeutics, addressing over 25 unique targets across more than 20 solid and blood cancer types, are currently in various stages of clinical development (566).

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 (509). Chemotherapy remains a backbone of cancer treatment, and its use is continually evolving to minimize potential harm to patients, while maximizing its benefits.

In June 2025, FDA approved a **mitomycin intravesical solution (Zusduri), the first gel-based chemotherapy for bladder cancer**, offering a novel nonsurgical approach that allows the chemotherapeutic to stay longer in the bladder and **significantly reduce tumor recurrence** in patients with non–muscle-invasive disease.



W47

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 evaluating the optimal dosage, novel formulations, treatment combinations, and sequence of chemotherapy delivery to improve patient outcomes.

As one example, a large international study that followed women with surgically resected, high-risk, early breast cancer for over 10 years to compare two chemotherapy schedules—one given every 3 weeks and one given every 2 weeks—found that the more frequent chemotherapy helped prevent breast cancer from coming back and improved overall outcome among this patient population (567). Another analysis found that people with pancreatic cancer who received their recommended chemotherapy regimen lived significantly longer than those who received lower than recommended dosage, suggesting that getting the recommended dosage of chemotherapy may improve survival (568). Yet another clinical trial conducted in France showed that among patients with advanced leiomyosarcoma, a rare tumor that develops in smooth muscle cells, those who received a combination of two chemotherapeutics, doxorubicin and trabectedin, followed by ongoing trabectedin lived longer than those who received doxorubicin alone (569).

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 **Addressing the Challenges Faced by Survivors**, p. 178). Researchers are investigating different approaches to making chemotherapeutics safer for patients. Areas of ongoing investigation include designing modifiable chemotherapeutics, such as those with "on" and "off" switches, that are selectively delivered to tumors while sparing healthy tissue, as well as evaluating less aggressive chemotherapy regimens that can allow patients the chance of an improved quality of life without compromising survival.

As an example, data from a recent clinical trial from China found that children with high-risk retinoblastoma did just as well with three cycles of chemotherapy as with six, but experienced fewer side effects, better quality of life, and lower treatment costs, supporting a shorter, less intensive treatment approach (570). Data from another clinical trial from the United Kingdom showed that among patients with early-stage anal cancer, reduced dosages of chemotherapy and radiotherapy showed similar short-term cancer control and fewer side effects compared to the standard-dose treatment, suggesting it may be a safer option while maintaining effectiveness (571).

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. To improve patient safety, FDA has recently updated drug labels to include information about this genetic risk and now recommends that clinicians consider testing patients for DPD deficiency before starting treatment (see **Rapidly Delivering Safe and Effective Therapies to Patients**, p. 216) (572).

Another particularly exciting area of clinical cancer research is the evaluation of circulating tumor DNA as a biomarker to identify cancer patients who are at a low risk of recurrence and can safely forgo postsurgical chemotherapy (see **Liquid Biopsy in Cancer Care**, p. 203) (573,574).

Advances in Treatment With Molecularly Targeted Therapeutics

Remarkable advances in our understanding of cancer biology, including the discovery of numerous cellular and molecular alterations that drive tumor growth, have ushered in a new era of precision medicine. 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. 29).

Therapeutics directed to molecules influencing cancer cell multiplication and survival target tumor cells more precisely than cytotoxic chemotherapeutics, which generally target all rapidly dividing cells, and thereby limit damage to healthy tissues. The greater precision of these molecularly targeted therapeutics tends to make them more effective and less toxic

SIDEBAR 34

The Increasing Precision of Molecularly Targeted Therapeutics

Research has increased understanding of the factors most associated with 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, with selected examples that have been approved by the US Food and Drug Administration (FDA):

Angiogenesis inhibitors

Block new blood vessel formation, which is vital for tumor growth and metastasis, for example, bevacizumab (Avastin).

Cell-lysis mediators

Cause cancer cell death via different mechanisms, for example, antibody-drug conjugates, such as trastuzumab deruxtecan-nxki (Enhertu), which deliver anticancer drugs specifically to cancer cells.

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 and 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, panobinostat (Farydak).

Hormones/Antihormones

Block hormones such as estrogen or testosterone that drive cancer development, for example, apalutamide (Erleada).

Proteasome inhibitors

Block the action of proteasomes, which are part of the normal cellular machinery for breaking down proteins. 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).

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.

than cytotoxic chemotherapeutics (see **Sidebar 34**, p. 107). As a result, they are not only saving lives but also allowing patients with cancer to have a higher quality of life.

Diagnostic tests, such as sophisticated DNA sequencing or protein visualizing methods, are commonly used in the clinic to identify molecular changes in patient's cancers (see **Sidebar 35**, p. 108), 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.

Unfortunately, because of multilevel barriers to health care, including inadequate health insurance and lack of access to quality cancer care, there are disparities in the utilization of diagnostic testing and molecularly targeted treatments (523,575). For example, despite overall increases in next-generation sequencing—a cutting-edge diagnostic testing method vital for making molecularly targeted treatment decisions—from 2015

SIDEBAR 35

Companion Diagnostics

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

Companion diagnostics:

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

Are **regulated** by the US Food and Drug Administration (FDA);

Accurately match patients with a specific therapy;

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

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

FDA approvals of **four** new molecularly targeted therapeutics during the 12 months covered in this report have been accompanied by the concurrent approval of companion diagnostic tests to facilitate the identification of eligible patients for these treatments.

Adapted from (577).

to 2022, rising from 19 percent to 27 percent in metastatic prostate cancer and from 14 percent to 47 percent in advanced urothelial cancer, significant disparities persist. Black and Hispanic patients, individuals with low socioeconomic status, those with Medicaid or government insurance, and people living in certain geographic regions remain consistently less likely to receive this testing (576).

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.

Highlighted in the following sections are the 15 new molecularly targeted anticancer therapeutics that were approved by FDA in the 12 months covered in this report, from July 1, 2024, to June 30, 2025 (see **Table 6**, p. 98).

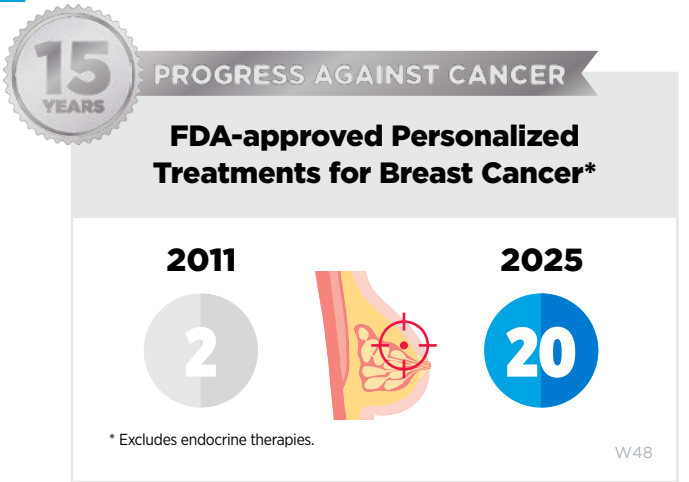
Although not discussed in detail, during the same 12-month period, FDA also expanded the use of four previously approved molecularly targeted therapeutics for treating new cancer types (see **Table 6**, p. 98). As an example, in January 2025, FDA approved the KRAS-targeted therapeutic sotorasib (Lumakras) in combination with the EGFR-targeted therapy, panitumumab (Vectibix), for adults with metastatic colorectal cancer that has a mutation known as KRAS G12C (see **Sidebar 36**, p. 109). Sotorasib was previously approved for certain patients with NSCLC (372).

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. However, breast cancer still ranks as the second leading cause of cancer death in US women (6). Furthermore, rates of invasive breast cancer have been steadily rising since the mid-2000s, with women younger than 50 experiencing the fastest increase, attributable in part to changes in lifestyle and/or hormonal risk factors (6). Therefore, continued innovation and investments in newer and more effective treatments are needed to address the evolving burden of the disease.

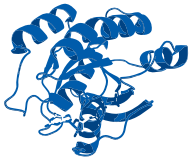
Two recent FDA decisions have the potential to further accelerate progress against breast cancer because they have provided new molecularly targeted treatment options for certain patients.

For patients with breast cancer, treatment decisions are often guided by the presence or absence of three key biomarkers—



SIDEBAR 36

Targeting the Undruggable KRAS



KRAS mutations are one of the most common genetic changes in cancer, found in about 90 percent of pancreatic cancer, 50 percent of colorectal cancer, and 30 percent of lung cancer patients, where they drive tumor growth by keeping the KRAS protein in an "on" state.

Long considered undruggable due to challenges in targeting KRAS, recent advances in cancer biology, computational science, and drug design have led the US Food and Drug Administration (FDA) to take the following regulatory actions:

2021

Sotorasib (Lumakras), the first KRAS-targeted therapeutic was approved. The approval was for patients with non–small cell lung cancer (NSCLC).

2022

Adagrasib (Krazati), the second KRAS-targeted therapeutic, was approved, also for patients with NSCLC.

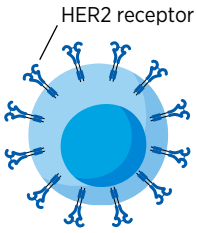
2024

Adagrasib was approved in combination with cetuximab, an EGFR-targeted therapy, for patients with colorectal cancer.

2025

Sotorasib was approved in combination with panitumumab, another EGFR inhibitor, for patients with colorectal cancer.

Ongoing research is exploring multiple new strategies to target KRAS across various additional cancer types, including new targeted therapies that inhibit additional *KRAS* mutations using different mechanisms, as well as immunotherapies such as KRAS-targeted cancer vaccines.



The **HER2 protein** (also called c-erbB-2, HER2/neu, human EGF receptor 2) **is involved in normal cell growth. Certain cancer cells**, including those of the breast, ovary, bladder, pancreas, stomach, and esophagus can **produce excessive amounts of HER2 leading to uncontrolled cell multiplication and spread**. Checking the amount of HER2 on cancer cells may help plan treatment.

Source: (578).

W49

estrogen and progesterone hormone receptors (HR), 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 (4). Treatment options for these patients include antihormone therapeutics, such as tamoxifen (prevents estrogen from attaching to its receptor), letrozole (lowers estrogen levels), or fulvestrant (destroys estrogen receptor), with or without another molecularly targeted therapy known as a cyclin-dependent kinase 4/6 inhibitor. Antihormone therapeutics, also known as endocrine therapy, work by reducing the hormonal signals that drive cancer growth and survival.

Unfortunately, most advanced HR-positive breast cancers that initially respond to endocrine therapy eventually progress because they have become treatment resistant (see **Sidebar 37**, p. 110). Identifying novel targets for the development of new and effective therapies for this patient population is an area of active investigation.

In January 2025, FDA approved a new treatment called datopotamab deruxtecan-dlnk (Datroway) for adults with advanced HR-positive/HER2-negative breast cancer that cannot be removed with surgery or that has spread to other parts of the body. The approval was for patients whose disease has progressed despite previous treatments with antihormone therapy and chemotherapy (see **Delivering Cytotoxic Agents Precisely to Cancer Cells**, p. 113).

Research has shown that a signaling pathway involving the protein PI3K-alpha and its partners is vital for normal cell multiplication and survival and is overactivated in approximately half of HR-positive/HER2-negative breast cancers (580). PI3K-alpha is a key component of the pathway and activating mutations in the *PIK3CA* gene, which provides the code that cells use to make the PI3K-alpha protein, are observed in 35 percent to 40 percent of HR-positive breast cancers (581). Overactivation of PI3K signaling in breast cancer has also been implicated in the development of resistance to endocrine therapy. A molecularly targeted therapeutic, alpelisib (Piqray), which blocks the function of PI3K-alpha protein, was approved for patients with breast cancer in 2019.

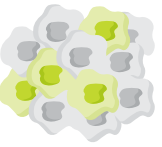
In October 2024, FDA approved a second PI3K-alpha inhibitor, inavolisib (Itovebi), in combination with a

SIDEBAR 37

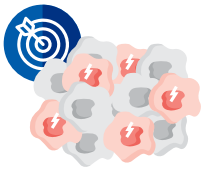
The Challenge of Treatment Resistance

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

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



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



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

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

Differences in tumor microenvironment components can render a treatment ineffective.

Adapted from (579).

cyclin-dependent kinase 4/6 inhibitor, palbociclib, and the endocrine therapy, fulvestrant, for adults with HR-positive/HER2-negative locally advanced or metastatic breast cancer that tests positive for *PIK3CA* mutation and has progressed during or after endocrine therapy. FDA also approved the FoundationOne Liquid CDx assay as a companion diagnostic test (see **Sidebar 35**, p. 108) to identify patients with breast cancer who are eligible for treatment with inavolisib.

Unlike alpelisib, inavolisib not only blocks PI3K-alpha function but also causes degradation of the protein. Researchers believe that this novel approach may improve the effectiveness of the treatment compared to alpelisib (582). FDA approval was based on results from a phase III clinical trial in which inavolisib combined with palbociclib and fulvestrant more than doubled the time patients lived without their cancer progressing compared to standard treatment (15.0 vs. 7.3 months) (581).

Matching Therapies to the Molecular Drivers of Lung Cancer

Lung cancer is the leading cause of cancer deaths in the United States. An estimated 226,650 new cases will be diagnosed, and 124,730 people will die from the disease in the United States this year alone (see **Table 1**, p. 18). More than 80 percent of lung cancers diagnosed in the United States are classified as NSCLC. Research over the past decade 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 (see **Figure 17**, p. 111). Thanks to these major advances in treatment, as well as improved prevention and earlier detection, the decline in lung cancer death rates has accelerated in the past decade. Between 2013 and 2022, lung cancer mortality rates fell by an average of 4.8 percent per year in men and 3.7 percent per year in women (6).

Dysregulation of the MET receptor protein plays a critical role in NSCLC by activating key processes including cell multiplication, survival, migration, and invasion. The MET receptor's interaction with its binding partner, hepatocyte growth factor, is vital for epithelial-to-mesenchymal transition (EMT), a hallmark of cancer development. In May 2024, FDA approved a MET-targeted therapeutic telisotuzumab vedotin-tllv (Emrelis) for adults with locally advanced or metastatic NSCLC with high MET overexpression who have received prior systemic therapy (see **Delivering Cytotoxic Agents Precisely to Cancer Cells**, p. 113).

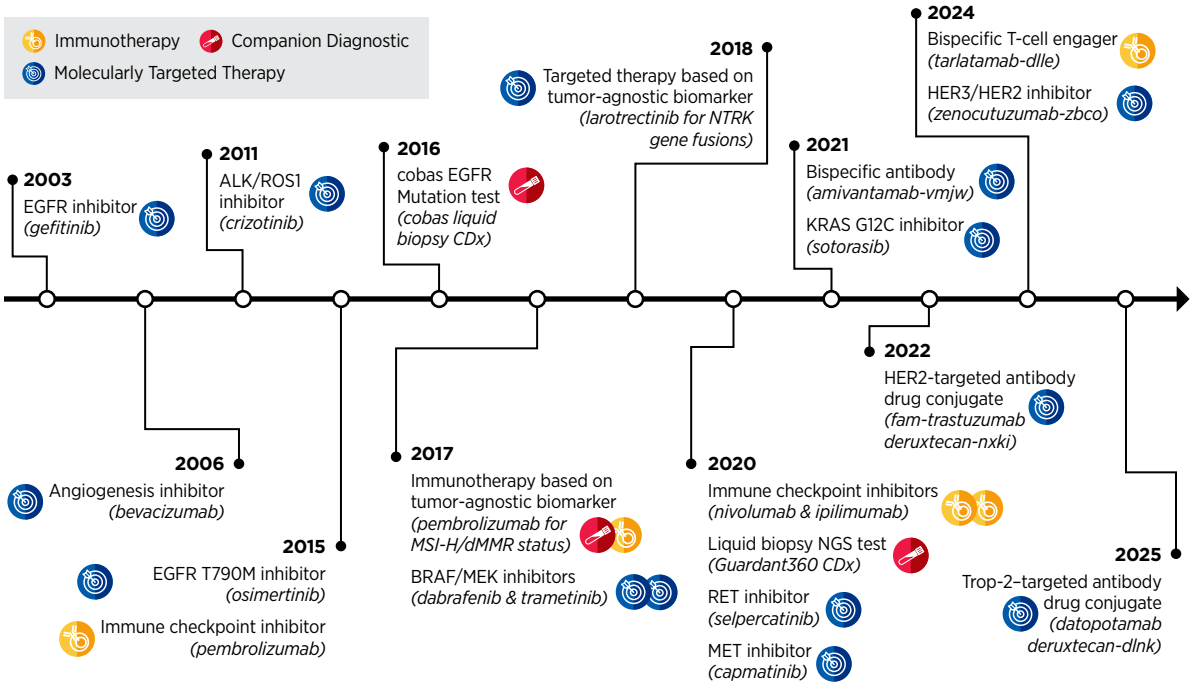
Alterations in the *EGFR* gene are found in 15 percent to 50 percent of advanced NSCLC cases (583). The most common EGFR mutations are deletions called exon 19 deletions and single base changes known as L858R substitutions (see **Sidebar 8**, p. 35). These mutations drive NSCLC growth and can be targeted with anti-EGFR therapeutics. However, most patients eventually become resistant to such treatments. In many cases, this resistance is linked to new mutations in *EGFR*, such as the single base change called T790M, or to activation of the MET pathway, though in many cases, the cause of resistance is still unknown.

Currently, the standard treatment for NSCLC patients with EGFR mutations is osimertinib (Tagrisso), an EGFR-targeted therapeutic, which specifically inhibits cancer-driving mutant

FIGURE 17

Precision Medicine 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*, and *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 US Food and Drug Administration (FDA) approvals for molecularly targeted therapeutics or immunotherapeutics that have distinct mechanisms of action.

forms of EGFR, including that produced by the EGFR T790M mutation, and has been shown to delay cancer growth better than earlier versions of EGFR-targeted drugs. Unfortunately, resistance to osimertinib arises in nearly all patients. Researchers are evaluating new therapeutics, alone or in combination, to address this challenge.

One such therapeutic is amivantamab-vmjw, which was approved by FDA in 2021 (372). Amivantamab-vmjw binds to both EGFR and MET on the surface of lung cancer cells and blocks the cancer-driving signals triggered by these proteins while also engaging the immune system to attack cancer cells. It has shown promise when used alone or with chemotherapy, especially in patients who have stopped responding to osimertinib. In August 2024, FDA approved a new EGFR-targeted therapeutic, lazertinib (Lazcluze), in combination with amivantamab-vmjw for the initial treatment of locally advanced or metastatic NSCLC with EGFR exon 19 deletions or L858R substitutions, as detected by an FDA-approved test.

Lazertinib is a highly selective EGFR-targeted therapeutic that can block mutant forms of EGFR including EGFR T790M. In addition, unlike most EGFR-targeted treatments, lazertinib can reach the brain and may be effective against lung cancer that has metastasized to the brain. Researchers hypothesized that the combination of amivantamab-vmjw with lazertinib would prevent the development of treatment resistance (583).

FDA approval was based on the results of a phase III clinical trial that compared the effectiveness of amivantamab-vmjw plus lazertinib to osimertinib and showed that the combination therapy reduced the risk of disease progression or death by 30

percent compared to osimertinib. NSCLC patients receiving the new combination lived nearly 7 months longer without their cancer worsening (24 months vs. 17 months) (583). Additional research is needed to identify effective strategies to manage and reduce the toxicities associated with the combination, and to evaluate whether the combination therapy can improve overall survival as well as its effectiveness in high-risk NSCLC patients, such as those with detectable circulating tumor DNA during treatment, coexisting *TP53* mutations, and brain or liver metastases.

Research has shown that *ALK* gene mutations fuel 3 percent to 11 percent of NSCLC cases (584). This knowledge has led to the development of several anticancer therapeutics targeting ALK. Crizotinib was the first of these to be approved by FDA, in August 2011, and became the standard initial treatment for patients with metastatic ALK-positive NSCLC. Unfortunately, not all patients with NSCLC driven by ALK have tumor shrinkage after crizotinib treatment. Moreover, the majority of patients whose cancer initially responds eventually experience relapse because the cancer becomes resistant to the agent. In many cases, crizotinib resistance emerges because NSCLC cells acquire additional ALK mutations.

These discoveries have led to the development of a new generation of ALK-targeted treatments, many of which are able to block the unique forms of ALK that result from these new mutations. In the past decade, FDA has approved four additional ALK-targeted therapeutics—ceritinib, alectinib, brigatinib, and lorlatinib—to treat ALK-positive NSCLC (585). These newer treatments are more effective than crizotinib, especially at reaching and treating NSCLC that has spread to the brain. Initially used only in patients who stopped responding to crizotinib, these newer drugs have now become the preferred first treatment because they help patients live longer.

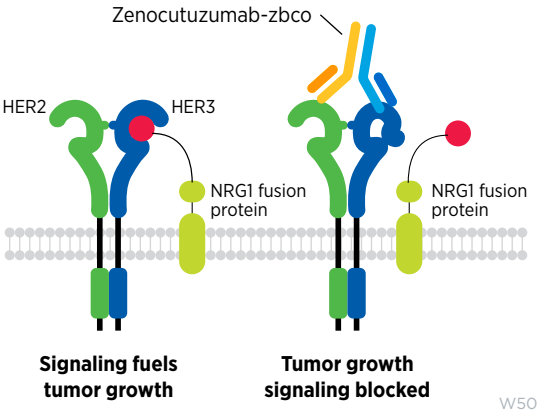
In December 2024, FDA approved the sixth ALK-targeted therapeutic, ensartinib (Ensacove) for patients with ALK-positive locally advanced or metastatic NSCLC who have not previously received an ALK-targeted therapy. The approval was based on the results of a phase III clinical trial showing that patients receiving ensartinib lived nearly twice as long without their cancer getting worse as those receiving crizotinib, 26 months versus 13 months. Ensartinib also worked better at treating brain metastases, a common concern in lung cancer. These data have established ensartinib as a potential new option for patients starting treatment for ALK-positive NSCLC.

Identifying which targeted therapy is most appropriate as the initial treatment for ALK-positive NSCLC and the order in which additional FDA-approved ALK-targeted therapeutics should be used to provide the maximum benefit for patients is an area of intensive research. A recent analysis comparing the effectiveness and safety of the six FDA-approved ALK inhibitors found that lorlatinib offers the greatest benefit in delaying disease progression, although it is associated with a higher risk of side effects (585). While some clinicians recommend using lorlatinib first, others prefer starting with alectinib, ceritinib, brigatinib, or ensartinib, which tend to have fewer side effects, and reserving lorlatinib for later treatment if the disease progresses. The overall goal remains to maximize treatment effectiveness while minimizing toxicity and improving long-term outcomes for patients. Additional research is needed to establish a clear consensus on the best sequence of these therapies.

The protein neuregulin 1 (NRG1) plays an important role in the development and maintenance of the nervous system and heart. In less than 1 percent of all solid tumors, structural variations (see **Sidebar 8**, p. 35) 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.

In December 2024, FDA approved zenocutuzumab-zbco (Bizengri) for patients with advanced, surgically unremovable, or metastatic NSCLC or pancreatic cancer harboring an *NRG1* gene fusion whose disease has progressed despite systemic treatments. Zenocutuzumab-zbco blocks the NRG1 fusion protein from promoting the pairing of HER2 and HER3 proteins, thereby turning off the cancer-promoting signaling cascade initiated by the HER2/HER3 complex. Zenocutuzumab-zbco is the first HER3-targeted therapeutic approved by FDA, bringing a new hope to patients, such as

How Zenocutuzumab-zbco Works



Bob Fortin (see p. 114), who previously had limited options for their difficult-to-treat cancer.

FDA approval was based on the results of a clinical trial in which one-third of patients treated with zenocutuzumab-zbco experienced tumor shrinkage that lasted a median of 11 months (586). Most patients in the study had either NSCLC or pancreatic cancer, and while zenocutuzumab-zbco shrank tumors in people with different cancers, those with NSCLC and pancreatic cancer were most likely to respond. More than 30 percent of patients with NSCLC and 40 percent of patients with pancreatic cancer experienced tumor shrinkage (586).

The study marks a significant step forward in treating cancers with NRG1 fusions by offering a new molecularly targeted option for patients who typically respond poorly to standard therapies. While the response rate of 30 percent is modest, the drug shows clear benefits, including low toxicity. Ongoing research aims to understand why some patients respond better than others and how resistance develops, with hopes of expanding the use of zenocutuzumab-zbco to more cancer types.

About 1 percent to 3 percent of NSCLCs are fueled by genetic alterations known as chromosomal translocations that involve the *ROS1* gene and lead to the production of ROS1 fusion proteins (587). These cancers often affect younger people, women, and those who have never smoked. In many patients, the cancer is diagnosed after it has already spread, including to the brain.

Several ROS1-targeted therapeutics have been approved by FDA, including crizotinib, entrectinib, and repotrectinib. However, these treatments have important limitations. Crizotinib is more effective than standard chemotherapy, but almost half of the patients treated develop brain metastases, which lead to poor outcomes. Many patients also become resistant to crizotinib attributable to newly acquired mutations in *ROS1* gene, known as G2032R. Entrectinib was designed to be able to reach the brain but showed limited effect in NSCLC patients with brain metastases or those with acquired G2032R mutations. Repotrectinib, approved by FDA in 2023, is more effective against brain metastases and G2032R mutation but may cause serious side effects, especially neurologic problems, such as dizziness and lack of coordination.

Therefore, the approval of the newest ROS1-targeted therapy, taletrectinib (Ibtrozi), in June 2025 brings new hope for adults with locally advanced or metastatic ROS1-positive NSCLC. Taletrectinib is an oral drug that has been shown to work well in the brain, remains effective against G2032R mutation, and has fewer neurologic side effects.

FDA approval was based on results from two international phase II clinical trials showing that taletrectinib helped shrink tumors in about 85 percent to 90 percent of NSCLC patients who had never received ROS1-targeted therapy before. Among those who responded, about two-thirds to three-quarters had responses that lasted at least 1 year. In people who had already been treated with other ROS1-targeted drugs, taletrectinib still shrank tumors in about 52 percent to 62 percent of patients.

Taletrectinib also worked well in patients with brain metastasis and those with resistance mutations like G2032R. The side effects were mostly mild, with low rates of dizziness and other brain-related symptoms. Because of its strong and lasting effects, brain activity, and favorable safety profile, taletrectinib is expected to become a leading treatment option for people with ROS1-positive advanced lung cancer.

Despite the emergence of numerous molecularly targeted therapeutics as groundbreaking new treatments for NSCLC, and the evidence showing that targeted treatments guided by molecular testing of the tumor yield superior outcomes for patients with NSCLC (588), molecular testing rates and targeted therapy use remain low and there are wide variations across health care practices (589,590). Broad implementation of cutting-edge molecular testing to identify therapeutically targetable genetic alterations driving NSCLC offers meaningful benefits to patients, is cost-effective, and must be a priority in cancer medicine (591).

Delivering Cytotoxic Agents Precisely to Cancer Cells

Two new anticancer treatments approved by FDA in the 12 months covered by this report belong to a class of molecularly targeted therapeutics known as antibody–drug conjugates (ADCs). ADCs consist of three main components: an antibody that specifically recognizes and binds to a target protein found mostly on cancer cell surface; a linker that connects the antibody to a chemotherapy; 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 cytotoxic chemotherapeutic compared with traditional systemic delivery.

Trop-2 is a cell surface protein involved in key signaling pathways that regulate cell growth and survival. Trop-2 levels are frequently elevated in many cancers, including breast cancer and lung cancer, where it promotes tumor growth and spread. Elevated Trop-2 levels in breast cancer, particularly in HR-positive/HER2-negative and HR-negative/HER2-negative (also known as triple-negative) subtypes, have been linked to worse survival, making it a promising target for new therapies.

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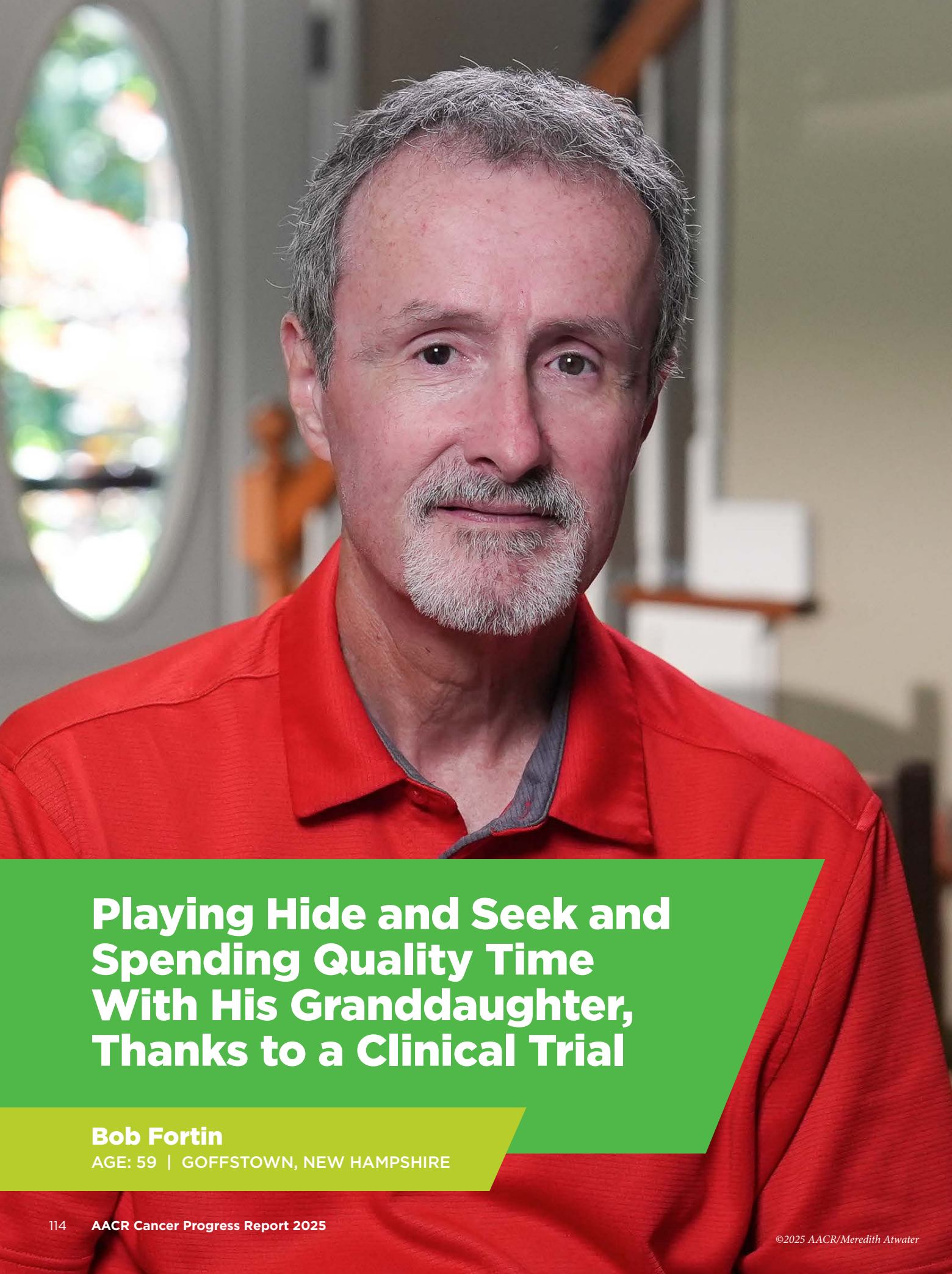

Playing Hide and Seek and Spending Quality Time With His Granddaughter, Thanks to a Clinical Trial

Bob Fortin
AGE: 59 | GOFFSTOWN, NEW HAMPSHIRE

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Bob Fortin had built a full life in Goffstown, New Hampshire. At 56, he was a husband of 37 years, a father of two, and a successful business owner for over 15 years. Life was structured, steady—until, in July 2022, when everything changed.

Bob began experiencing persistent digestive issues. At first, he chalked it up to stress; his daughter was soon to be married. But his condition worsened. "I wasn't digesting my food properly," he recalled. "Things kept escalating." Repeated visits to his doctor yielded temporary solutions—antacids, antibiotics—but nothing worked for long. Finally, frustrated and insistent, Bob demanded deeper testing.

Bloodwork revealed extremely high liver enzymes. A referral to Dartmouth Hitchcock Medical Center led to further imaging and a biopsy. On the eve of his 57th birthday, Bob received the daunting diagnosis: pancreatic cancer. He was alone when the call came. "I preferred it that way," he said. "It gave me space to take it in."

The news devastated his family. "My wife, my kids—we were all a mess," he recalled. "You Google pancreatic cancer, and it doesn't give you much hope."

Despite the grim reputation of pancreatic cancer, Bob's doctors initially offered optimism. His tumor was resectable, and he embarked on a rigorous treatment plan. From November 2022 to May 2023, he underwent 12 rounds of chemotherapy, intensive radiation, followed by a Whipple procedure, a major surgery to remove the tumor.

After the surgery, which was followed by more chemotherapy, Bob entered what seemed like a hopeful remission. Routine scans every 8 weeks showed the cancer had not spread. He returned to golf, yard work, and time with his infant granddaughter. But by July 2024, a scan revealed new lesions in his liver. The cancer had returned and had metastasized. Bob was told he had roughly 10 months to live.

Bob started receiving additional chemotherapy but that didn't help. At his family's insistence, Bob sought second opinions for the treatment options for the devastating diagnosis of stage IV pancreatic cancer. He visited Memorial Sloan Kettering Cancer Center, Mayo Clinic, and Dana-Farber Cancer Institute.

Those second opinions identified a key molecular detail: Bob had a rare subtype of pancreatic cancer. When Bob met with his physician at the Mayo Clinic, he recommended a clinical trial at Dana-Farber evaluating a promising investigational drug, zenocutuzumab-zbco (Bizengri), which targeted his tumor's rare genetic mutation. "He was the first doctor to give us hope," said Bob. The doctors at Memorial Sloan Kettering affirmed the recommendation.

In December 2024, Bob began receiving the trial therapy—he refers to as "the Z drug"—at Dana-Farber. Unlike his earlier treatments, this therapy had virtually no side effects. "I'd go in for my infusion, and the next day I'm mowing the lawn or playing golf," he said. "Before, chemo would knock me out for days."

Since the start of the trial, Bob has received 15 infusions of zenocutuzumab-zbco. His cancer is now stable, with minor tumor shrinkage and no new spread. Scans every 8 weeks continue to show tumor control, and he reports steady weight gain, increased energy, and improved digestion. "I've put back on 10 of the 40 pounds I lost," he said. "That has not happened in years. This drug did not just stabilize the cancer. It gave me back my life."

Dr. James M. Cleary, Director of Clinical Research in the Division of Gastrointestinal Oncology at Dana-Farber, is very optimistic. "If this genetic alteration hadn't been found, Mr. Fortin would've faced chemotherapy, which I don't believe would have been as effective or as tolerable as the targeted therapy he's on now. It's been incredible to see him not only respond but truly live a full life."

The emotional arc of Bob's journey is anchored in family. His daughter, moved by his diagnosis, accelerated plans to start a family. Just three months after Bob's initial diagnosis, she became pregnant. "She never said it outright, but I know she wanted to make sure I'd meet my grandchild," he said. Now, that granddaughter is the center of his world.

"We play hide and seek, take wagon rides, mow the lawn together," he said. "My wife says I'm her favorite person—and I believe it."

Bob credits his family not just with emotional support, but with saving his life. "They were the ones who refused to give up. They pushed for second opinions, for more options," he said. "Without them, I don't think I'd be here."

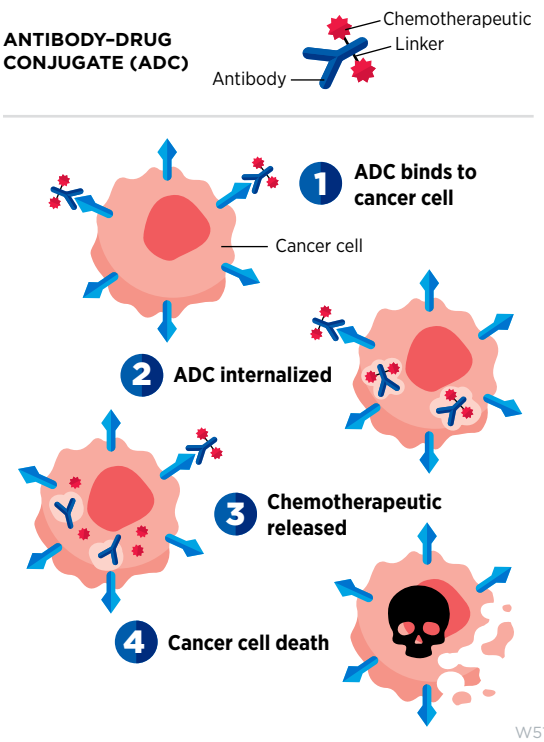
That refusal to quit now fuels his message to the public and to policymakers. "We see our government spending money everywhere," he said. "But if this was your diagnosis, wouldn't you want to know there was something left to try?"

Bob's message to our lawmakers is clear: Federal funding for cancer research is not optional. It is lifesaving. "This clinical trial gave me more time. It gave me a future. But that only happens when research gets funded."

"We've got to beat this disease. And the only way to do that is by funding research."

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

How Do ADCs Work?



Datopotamab deruxtecan-dlnk is an ADC comprising the cytotoxic agent, deruxtecan, attached to a Trop-2–targeted antibody by a linker. In January 2025, datopotamab deruxtecan-dlnk was approved by FDA for the treatment of adult patients with unresectable or metastatic, HR-positive/HER2-negative breast cancer who received prior endocrine-based therapy and chemotherapy. Datopotamab deruxtecan-dlnk is the second Trop-2–targeted ADC to receive FDA approval for breast cancer patients; the first, sacituzumab govitecan-hziy (Trodelvy), was approved in April 2020 for adults with metastatic triple-negative breast cancer (592).

FDA approval was based on results from a phase III clinical trial showing that patients who received datopotamab deruxtecan-dlnk lived longer without their cancer getting worse—nearly 7 months compared to 5 months for those who received standard chemotherapy (593). Additionally, treatment with datopotamab deruxtecan-dlnk, compared to chemotherapy, was associated with fewer side effects. However, more research is needed to show whether the new therapeutic can extend overall survival compared to chemotherapy. Researchers are currently evaluating the effectiveness of datopotamab deruxtecan-dlnk, alone or in combination with other treatments, in additional subtypes of breast cancer, including the type **Michelle Anderson-Benjamin** (see p. 118) was diagnosed with (594–596).

In June 2025, FDA expanded the approval of datopotamab deruxtecan-dlnk to include the treatment of adults with advanced or metastatic NSCLC that has a mutation in the *EGFR* gene, the most common mutation in NSCLC, and has progressed after an EGFR-targeted therapy and platinum-based chemotherapy. The approval was based on results from two clinical trials showing that datopotamab deruxtecan-dlnk shrank tumors in 45 percent of patients (597).

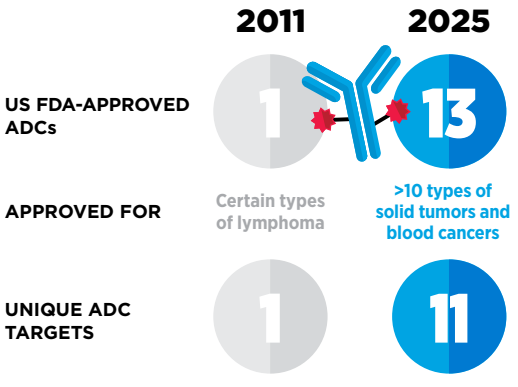
The second ADC approved by FDA during the 12 months covered by this report is telisotuzumab vedotin-tllv. It was approved in May 2024, for adults with locally advanced or metastatic NSCLC who have received prior systemic therapy and whose cancers have certain biomarkers known as high MET overexpression. FDA also approved the VENTANA MET (SP44) RxDx Assay as a companion diagnostic test to identify NSCLC patients who are eligible for treatment.

Three types of alterations in the MET protein are observed in NSCLC: Mutations (known as exon 14 skipping mutations) in the *MET* gene, seen in about 2 percent to 4 percent of patients; extra copies of the *MET* gene (known as gene amplification), seen in about 5 percent of patients; and excessive amounts of MET protein (known as MET overexpression), seen in up to 40 percent of patients (598). These alterations can help tumors grow and resist treatment, making MET a critical target for precision therapies in NSCLC.

MET overexpression may occur alone or coexist with other MET alterations and is linked to worse outcomes for patients. Based on the abundance of the protein, MET overexpression in NSCLC patients is classified as absent, low, intermediate, or high.

15 YEARS PROGRESS AGAINST CANCER

Antibody–drug Conjugates (ADCs)



Telisotuzumab vedotin-tllv is the first FDA approved ADC to target MET-overexpressing cells and the second to be approved for patients with NSCLC. It comprises a cytotoxic agent, monomethyl auristatin E (MMAE), attached to an MET-targeted antibody by a linker. Telisotuzumab vedotin-tllv specifically binds to MET protein with high affinity, facilitating the targeted delivery of MMAE directly to tumor cells and leading to their destruction. FDA approval was based on data from a phase II clinical trial in which 35 percent of patients with high MET overexpression saw their tumors shrink in response to the treatment (598).

ADCs are the fastest-growing therapeutic approach for solid tumors worldwide. In 2024, 284 clinical trials were launched globally, nearly 100 more than in 2023, highlighting the rapid acceleration of research in this field (451). Ongoing investigation is focused on improving linker stability, identifying novel targets, and developing more potent payloads to enhance the precision, durability, and applicability of ADCs across a broader range of cancers.

Innovating Ovarian Cancer Treatment Through a Novel Combination

An estimated 20,890 new cases of ovarian cancer will be diagnosed in the United States in 2025, and 12,730 women will die from the disease (6). Low-grade serous ovarian cancer (LGSOC) is a rare and distinct form of ovarian cancer, accounting for less than 10 percent of cases. Compared to high-grade serous ovarian cancer, patients with LGSOC are usually diagnosed at a younger age but have better survival (599). Additionally, unlike high-grade ovarian cancer, LGSOC typically has normal *BRCA* and *TP53* genes but shows frequent changes in the RAS, RAF, and MAPK signaling pathways that affect how cells grow and divide.

Standard treatments used for other ovarian cancers, such as chemotherapy and molecularly targeted therapy, often have limited effectiveness in LGSOC and can cause significant side effects. This means patients with LGSOC often undergo many lines of treatment, and because they have longer survival, patients often face ongoing health challenges over time. There were no FDA-approved treatments specifically for LGSOC until this year. This changed in May 2025, when FDA approved a combination of two novel molecularly targeted therapeutics, avutometinib (Avmapki) and defactinib (Fakzynja), for patients with KRAS-mutated LGSOC that has returned after prior systemic treatment.

The RAF proteins and their signaling mediator, MEK, play a critical role in cell growth and drive many cancers including LGSOC. Molecularly targeted therapeutics that target RAF and MEK individually have been approved by FDA and are used in combination for treating several cancer types. Avutometinib is a new type of molecularly targeted therapeutic, referred to as a molecular clamp. It works by binding MEK and RAF together in a way that keeps them inactive (600). By gluing MEK and RAF together, avutometinib blocks both proteins at once and shuts down the RAF/MEK signaling pathway more efficiently.

Defactinib blocks another key protein called focal adhesion kinase (FAK), which supports cancer cell growth, survival, and spread (600). Upregulation of FAK signaling can also serve as a compensatory backup pathway that cancer cells use to resist treatment with RAF and MEK inhibitors. By shutting down FAK signaling, defactinib can slow cancer progression and make tumors more responsive to avutometinib.

FDA approval was based on results from a phase II clinical trial showing that the combination treatment shrank tumors in 44 percent of patients (601). This new combination is now providing effective treatment for patients such as **Mary Catherine Riley** (see p. 120).

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. Rare cancers can be challenging for researchers to study and for physicians to treat (see **Sidebar 38**, p. 122). 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.

Tenosynovial giant cell tumors are a group of rare tumors that arise in and around the joints and tendons. These tumors are benign, but they cause damage to the joints, which leads to pain, swelling, and limitation of joint movement. Surgery is the main treatment option. If patients do not have surgery or if the tumor continually recurs, patients suffer damage and degeneration of the affected joint and surrounding tissues or structures. In some cases, this can cause significant disability.

Research has shown that some cells in tenosynovial giant cell tumors have genetic alterations, called chromosomal translocations (see **Sidebar 8**, p. 35), that lead to overproduction of the protein CSF1, which attracts large numbers of immune cells to the site of the tumor. The immune cells that accumulate form the bulk of the tumor and cause inflammation and damage to surrounding tissue. Vimseltinib (Romvimza) is a new molecularly targeted therapeutic that specifically inhibits the function of CSF1R, the protein on the surface of immune cells that CSF1 attaches to (603).

continued on page 122

Redefining What It Means to Live With Stage IV Triple-Negative Breast Cancer

Michelle Anderson-Benjamin
AGE: 41 | NEW YORK, NEW YORK

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Michelle Anderson-Benjamin had always been the backbone of her family. A mother of two in New York City, a health care administrator by profession, and a longtime caregiver and advocate for others, she was used to being the one people turned to. But in September 2020, at age 36, her world flipped when she was diagnosed with stage I triple-negative breast cancer (TNBC)—a highly aggressive form of the disease disproportionately affecting younger Black women.

The first sign came during the COVID-19 lockdown. While remote schooling her kids and working from home, Michelle noticed blood leaking from her right breast. Her gynecologist initially suspected an infected cyst or complications from a recent IUD insertion, but the symptoms didn't go away. A visit to the ER led to an ultrasound and urgent follow-up testing at Memorial Sloan Kettering Cancer Center. By the following week, she had undergone five biopsies, an MRI, and consultations with a breast surgeon. "I hoped I wouldn't hear the words, 'You have cancer.' But I was also prepared," said Michelle.

Even as a health care worker and caregiver to other cancer patients, the moment hit hard. But Michelle didn't freeze. "When the doctor came back after those 5 minutes to let me absorb the news, I pulled out my binder and said, 'Let's get to work.'"

She had already researched her subtype, her options, and potential clinical trials. She insisted on choosing her own care team. "I needed to fight the way I knew how. I didn't want anyone else scripting my story."

Her initial treatment began with a unilateral mastectomy in October 2020, with placement of a tissue expander. Complications followed—her body rejected the implant twice, resulting in nine surgeries before chemotherapy could even begin. Eventually, she underwent multiple cycles of AC-T chemotherapy—Adriamycin (doxorubicin), cyclophosphamide, and Taxol (paclitaxel), with adjustments along the way due to vein issues and side effects. She "rang the bell"—celebrating successful treatment—in May 2021.

But in October 2022, 2 years after her initial diagnosis, the cancer had recurred, and Michelle was diagnosed with stage IV metastatic TNBC. There was no gradual escalation; she had jumped from stage I to stage IV without warning. "It was like climbing one step and suddenly finding yourself dangling off the top ledge."

At the time of recurrence, there were few treatment options. Michelle did not qualify for immunotherapy due to not having the biomarker, PD-L1, that is required to be eligible for treatment or for HER2–targeted treatments, since her tumor was HER2-negative. But then a clinical trial opened, a phase III study testing an antibody–drug conjugate datopotamab deruxtecan-dlnk (Datroway) for metastatic TNBC. She enrolled and began what would become a transformative journey.

Today, Michelle has completed 40 cycles of the investigational treatment, which is now approved for certain other forms of breast cancer. She is believed to be the top patient on the trial in terms of duration and response. Her scans currently show no evidence of cancer.

Despite its effectiveness, the treatment comes with taxing side effects, including severe dry eye, joint pain, and dry mouth. Michelle mitigates these through a strict routine: She eats clean, takes vitamins, practices yoga, lifts weights, and attends biweekly massages. "I can't pour into others unless my cup is overflowing," she said. "And I plan to be the healthiest, sexiest 40-something in the room."

Her strength is rooted in her father's wisdom. "He used to say, 'You've got 5 minutes to cry. On the sixth minute, I want a solution.' That's how I live." After her father's passing, whom she lovingly cared for in ICU for 3 months, Michelle leaned even harder into her advocacy work.

She founded The Fearless Warrior Project, an organization focused on helping people facing cancer prioritize their mental health, legacy, and self-worth. Its logo is inspired by a photo of her young daughter playing superhero in the living room. "I wanted my kids to see their mom face down this storm and still shine," she said. "If I can't change this story, at least my kids can say: my mom didn't back down."

As part of the project, Michelle writes and speaks nationally about survivorship, health equity, and legacy planning. One of her proudest moments was contributing a chapter to the best-selling book "A Mother's Prayer"—a letter to her daughter to be opened at age 23, when she begins early mammograms due to elevated genetic risk. "I couldn't walk her through her first mammogram if I'm not here—so I left her the words anyway."

To policymakers, her message is blunt: "We fight to stay alive every single day. We vote for you, we show up. Now we need you to show up for us. Fund the research. Don't wait for cancer to hit your family to care."

Michelle isn't asking for miracles, just for momentum. "We're not asking for handouts. We're asking for tools. Give us the science. Give us the trials. Give us the choice." And above all: "Remember, we didn't choose cancer. But we are choosing to live. Make it possible for us to keep choosing."

"Give us the science. Give us the trials. Give us the choice."

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

Living Cancer Free Thanks to a Precision Medicine Clinical Trial

Mary Catherine Riley
AGE: 53 | BELLEVILLE, ILLINOIS

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In 2019, Mary Catherine Riley—a fifth-grade special education teacher from Belleville, Illinois—was living a full and active life. At 46, she was a devoted mother to a 9-year-old son and a 16-year-old daughter. She loved hiking, biking, yoga, and creating art, and she was in excellent health. That changed when she began experiencing persistent bloating and urinary frequency.

Initially, her symptoms were dismissed as minor. But when she visited her gynecologist in June 2019, he immediately ordered an ultrasound and an OVA1 test, both of which suggested something serious. A CT scan confirmed a mass on her ovaries with signs strongly indicative of ovarian cancer. "Once you hear that diagnosis, it's devastating. I was pretty sure bad things were going to happen," Mary said.

Mary's partner at the time had lost his mother to ovarian cancer and recommended a trusted specialist, Dr. Premal Thaker, at Siteman Cancer Center at Barnes-Jewish Hospital and WashU Medicine in St. Louis. Mary called Dr. Thaker's office directly and within days had an appointment and a treatment plan. Dr. Thaker confirmed the diagnosis: stage III ovarian cancer, already present in the lymph nodes.

Before surgery, Mary's mind was flooded with worst-case scenarios, from a colostomy bag to permanent lifestyle changes. But Dr. Thaker's calm confidence gave her hope. The surgery revealed that her cancer was low-grade serous ovarian cancer—less aggressive than the high-grade form but with a high likelihood of recurrence and no established treatments.

Initially, Dr. Thaker thought Mary might avoid chemotherapy, but final pathology results showed otherwise. Mary underwent 6 rounds of chemotherapy from August through November 2019. She arranged her treatments around her school schedule, often teaching right up to the infusion days and returning to class soon afterward. "The nurses told me I probably wouldn't be teaching by the end, but I did. I only took off on chemo days."

Her school district rallied behind her, organizing fundraisers, wearing "Good Vibes" T-shirts, and even installing extra sanitizing stations. Her students, often assumed to be too young for compassion, surprised her with unwavering support. The side effects were manageable: hair loss, fatigue, and "chemo brain," but she maintained her daily routines and active lifestyle.

When chemotherapy ended, Mary showed no evidence of disease. To help prevent recurrence, her care team prescribed anastrozole, an estrogen-blocking drug typically used for breast cancer, the only available option for her tumor type. For three years, regular CT scans revealed stable results, until a lymph node grew large enough to be biopsied in 2023.

The biopsy confirmed the cancer had returned. Dr. Thaker recommended a clinical trial involving two targeted drugs, that later became known as avutometinib and defactinib. Mary agreed without hesitation, despite being warned about the time commitment: frequent blood draws, CT scans, and follow-ups. "If it's a chance to help me, I'll do it," she thought.

The treatment worked better than anyone anticipated. Within a year, she had a complete response. Side effects—skin rashes, vision changes, fluid retention, and fluctuating lab values—were persistent but manageable with supportive care and dose adjustments. "Yes, the side effects were annoying. But I don't have cancer right now. That's worth it."

Mary stayed on the trial for 2 years. She forged close relationships with her nurse, pharmacist, and other members of the study staff, all committed to advancing treatment for a cancer type that previously had no effective therapy. In May 2025, the drugs received FDA approval, and Mary transitioned from the trial to receiving the medications through a pharmacy.

Today, Mary continues taking the medication, now available as an FDA-approved combination called Avmapki Fakzynja Co-pack, with quarterly CT scans and monthly labs. She continues to have no evidence of disease.

Her children have grown up with her cancer journey as part of their family story. Her daughter, now in the medical field, often asks about the science behind her treatment. Both take pride in her role in a trial that has changed the future for others with low-grade serous ovarian cancer.

Outside of treatment, Mary continues to embrace life: traveling to see family; hiking any chance she gets; practicing yoga and meditation; drawing and painting. She has learned to live day by day, appreciating the small moments.

To members of Congress, she emphasizes the importance of federal funding for cancer research, not only for cancers like hers but for the wide spectrum of diseases that touch nearly every family. She sees her story as a call to action for more doctors to know about, and more patients to access, emerging treatments.

"Everyone is touched by cancer in some way," she said. "Funding research means more options, more time, and more hope for people like me."

"For my type of cancer, there was no treatment. Now there is, because of research."

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

SIDEBAR 38

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** (602).
- **All childhood cancers** are considered rare cancers.
- Rare cancers pose **significant challenges to patients, physicians, and researchers**.

According to the National Cancer Institute (NCI), these challenges include the following:

FOR PATIENTS

FINDING A PHYSICIAN

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

TREATMENT PROXIMITY

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

LONG DIAGNOSIS TIME

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

FOR PHYSICIANS

LACK OF TRAINING

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

UNSURE EXPECTATIONS

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

FINDING EXPERT HELP

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

FOR RESEARCHERS

LACK OF INFORMATION

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

LACK OF RESEARCH MODELS

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

LACK OF BIOSPECIMENS

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

LACK OF PATIENTS

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

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 for rare cancers in children, teens, and young adults faster.

Vimseltinib works by locking CSF1R in an inactive state, preventing it from turning on and sending signals that fuel tumor growth and inflammation.

Vimseltinib was approved in February 2025 for adults with symptomatic tenosynovial giant cell tumors for which surgical resection may cause worsening functional limitations or severe morbidity. The approval was based on results from a phase III clinical trial showing that 40 percent of patients had significant tumor shrinkage, compared to none in the placebo group (604). Patients also experienced meaningful improvements in joint movement, physical function, and pain relief, with most responses lasting at least 6 months.

Vimseltinib is the second CSF1R-targeted therapeutic approved for treating tenosynovial giant cell tumors. The first, pexidartinib, was approved in 2019. However, a unique mechanism of action of vimseltinib is attributable to a greater selectivity for CSF1R and fewer adverse effects, providing a potentially safer option for patients.

Biliary tract cancers are a group of tumors that develop in the organs involved in producing, storing, and transporting bile for digestion, namely, the gallbladder, bile ducts, or the area where the bile and pancreatic ducts meet the small intestine. These cancers are rare—affecting approximately 12,610 individuals in 2025—but typically diagnosed at advanced stages when surgery is no longer an option. Systemic therapies, therefore, are the mainstay of treatment for most patients. Chemotherapy regimens have long been approved to treat advanced biliary tract cancers, while in recent years, immunotherapy and molecularly targeted therapies have been added to the treatment landscape. Despite these advances, many patients with biliary tract cancers eventually relapse, underscoring the need for more effective personalized treatment strategies.

Research has shown that HER2 alterations are common in biliary tract cancer, present in up to 31 percent of gallbladder cancer cases, 19 percent of bile duct cancers in the liver, and 5 percent of bile duct cancers outside the liver (605). These findings suggest that HER2 targeting may potentially benefit these patients. In November 2024, FDA approved zanidatamab-hrii (Ziihera), a new HER2-targeted therapy, for patients with advanced or inoperable HER2-positive biliary tract cancer who have already received chemotherapy. This is the first HER2-targeted therapy approved for this rare cancer and brings new hope to patients such as **Dawn Varrati** (see p. 124). FDA approval was based on results from a phase II clinical trial, in which over half of the patients responded to the drug, with responses lasting nearly 15 months.

Zanidatamab-hrii is an engineered protein called a bispecific antibody that binds to two distinct regions of the HER2 protein. This dual binding helps block cancer-promoting signals, promotes HER2 receptor degradation, and enhances the immune attack on cancer cells to more effectively treat HER2-positive tumors.

Bringing the Promise of Precision Medicine to Children, Adolescents, and Young Adults With Cancer

In the United States, an estimated 9,550 children (ages 0 to 14 years) and 85,480 adolescents and young adults (AYA; ages 15 to 39 years) will be diagnosed with cancer in 2025 (4). Enormous progress has been made in the treatment of childhood and AYA cancers over the past several decades, as reflected in the greater than 85 percent 5-year relative survival rates for all cancers combined for both populations (see **Figure 2**, p. 17). In the 12 months covered in this report, FDA approved a number of new therapeutics that will continue the momentum of progress against pediatric and AYA cancers.

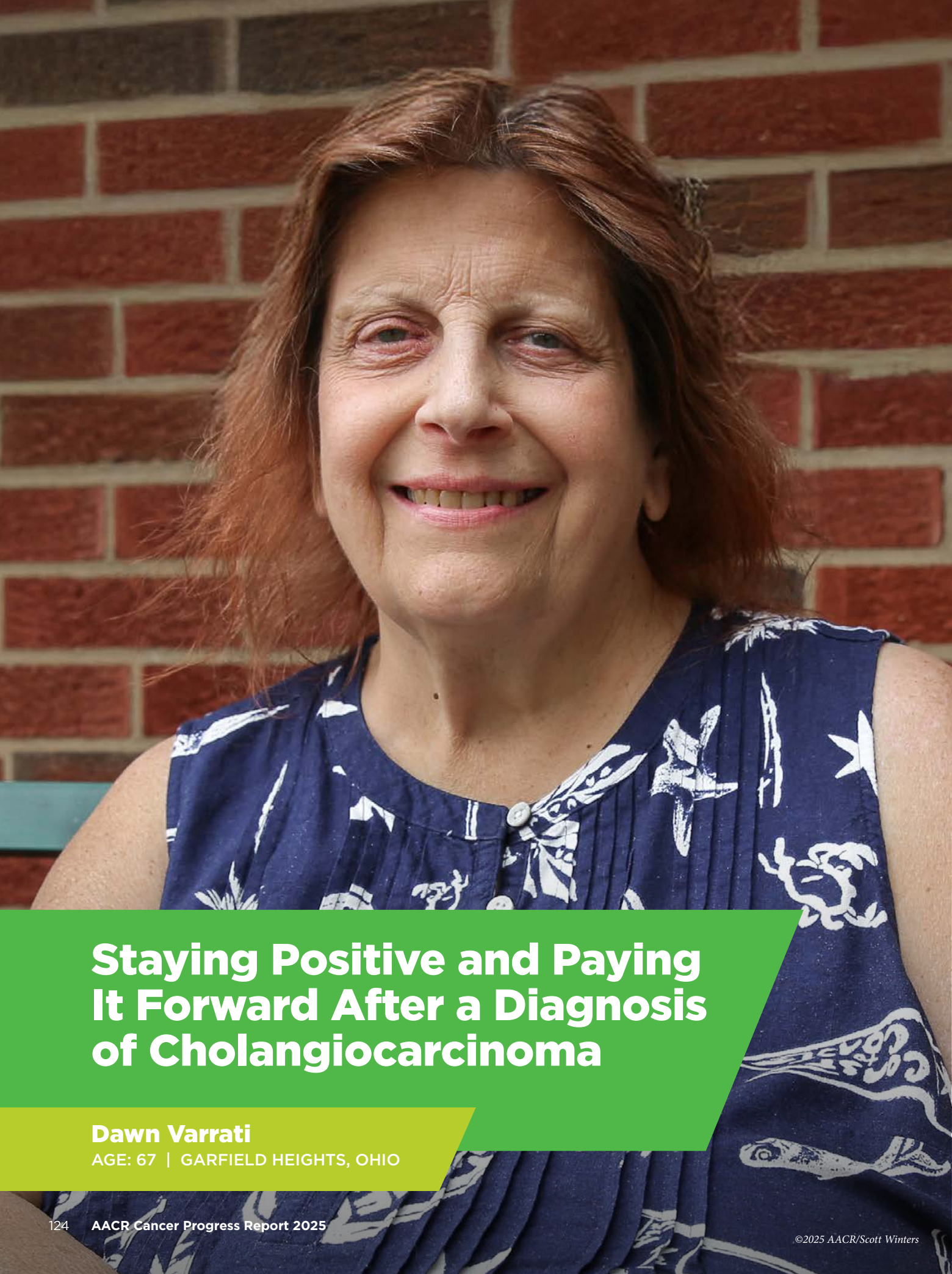
Brain and other nervous system tumors are the second leading cause of cancer deaths among AYA. Low-grade gliomas are slow-growing brain tumors. They can often be cured with surgery alone, but depending on their location, some low-grade gliomas cannot be fully removed if they are adjacent to vital structures in the brain. In some cases, low-grade gliomas may grow back even after surgical removal. Low-grade gliomas with mutation in the *IDH1* or *IDH2* genes are the most common malignant primary brain tumors diagnosed in young adults, such as **Alex Hepner** (see p. 126), a young adult who was diagnosed with this cancer (606). Patients with IDH mutant gliomas often receive a combination of radiation and chemotherapy after surgery, especially if they are at high risk of disease progression. While this regimen can keep the cancer in check for years, it is not curative and can lead to serious long-term side effects.

Research has shown that mutations in the *IDH1* or *IDH2* genes and subsequently abnormal IDH1 and IDH2 proteins lead to the production of an abnormal molecule called 2-hydroxyglutarate, which causes widespread epigenetic changes that disrupt normal cell function and drive brain tumor development (see **Epigenetic Changes**, p. 40) (607–610). These findings led to the investigation of therapeutic approaches for treating IDH1 and IDH2 mutant brain tumors by blocking the production or effects of 2-hydroxyglutarate. Building on this work, scientists developed the molecularly targeted therapeutic vorasidenib (Voranigo), which blocks the altered IDH1 and IDH2 proteins and substantially reduces levels of 2-hydroxyglutarate and associated epigenetic changes related to *IDH* mutations (611).

In August 2024, vorasidenib was approved by FDA for patients 12 years and older with certain slow-growing gliomas, known as grade 2 astrocytoma or oligodendroglioma, that have *IDH1* or *IDH2* mutation, after patients have undergone surgery, whether a full removal, partial removal, or just a biopsy of the tumor. FDA approval was based on results from a clinical trial showing vorasidenib significantly delayed tumor progression and the need for additional treatments. Patients who received vorasidenib had a 61 percent lower risk of tumor progression compared to those who received a placebo (611). Ongoing research is evaluating potential mechanisms of resistance to vorasidenib as well as its effectiveness in combination with immunotherapy.

Neurofibromatosis type 1 (NF1) is an inherited genetic disorder that causes severe symptoms and complications including a significantly increased risk for developing various types of tumors (see **Figure 6**, p. 36). Although the tumors that develop in

continued on page 128



Staying Positive and Paying It Forward After a Diagnosis of Cholangiocarcinoma

Dawn Varrati
AGE: 67 | GARFIELD HEIGHTS, OHIO

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At 63 years old, Dawn Varrati was navigating life after loss. A longtime Ohio resident, she got married at 37 and spent two joyful decades with her husband before he passed away. She stayed active, surrounded by close friends, some dating back decades, enjoying music, concerts, and lively outings. Life was good, not perfect, but fulfilling and she was looking forward to ongoing adventures with her friends.

Then, one day in July 2021, while grocery shopping with a neighbor, Dawn felt short of breath. "My lips were turning blue," she remembered. "They called the ambulance, and I remember hearing the sirens, I was holding on, waiting for them to come." Moments later, she collapsed. "I died right there," she said.

At the hospital, doctors initially attributed her condition to a previously diagnosed heart valve issue. But while preparing for valve replacement surgery at the Cleveland Clinic, routine preoperative scans found something unexpected on her liver. Further testing confirmed cholangiocarcinoma, also known as bile duct cancer.

Dawn's first reaction was dread. "You hear the word cancer, and everything else goes blank," she said. "I thought, 'This is it, I have to start saying goodbye.'" But her oncologist refused to let her spiral. "It's not like it used to be," he told her. "We have options now. We're going to fight this as aggressively as it's coming for you."

Dawn was ready to do what it took to beat the cancer.

"I told him, we're going to kick cancer's butt—and he liked that attitude," she said.

Her initial treatment began with a liver resection—surgeons removed 70 percent of the right lobe. Because the remaining cancer in the left lobe couldn't be surgically removed without causing liver failure, she underwent targeted radiation therapy. Later, she began several cycles of capecitabine, an oral chemotherapy that left her ill but temporarily cleared the disease.

But her cancer returned.

For the next few years, Dawn cycled through a wide range of treatments—radiation, multiple chemotherapies, and a form of targeted therapy, the latter based on a specific gene mutation. The targeted therapy kept her cancer stable for 11 months before, once again, the disease began to progress.

This time, the outlook was more sobering. Nonetheless, her doctor researched potential options for Dawn. There was an investigational targeted therapy, zanidatamab-hrii, being evaluated in a clinical trial that appeared to be her best, and only, option. "My doctor said, 'If you don't have this mutation, there may not be anything left for us to try,'" Dawn recalled.

"He told me I might only have 3 or 4 months. And that was the one time I cried. I thought, 'This is it.'"

However, Dawn had the biomarker that made her an eligible candidate for the treatment. In the meantime, zanidatamab-hrii (Ziihera) emerged from clinical trials and received FDA approval. Dawn heard back from her physician. "He said, 'I've already checked—your insurance approved it, and I think you'd be a perfect candidate,'" Dawn remembered.

Dawn became one of the first patients in the United States to receive the newly approved therapy outside of clinical trials. "Everyone was watching me during that first infusion," she said. "I joked, 'Am I the guinea pig?' and they said, 'No—you're the pioneer.'"

Dawn began treatment in early December 2024. Since then, she's experienced virtually no side effects beyond a manageable steroid-induced glucose spike, which is controlled through her endocrinologist. Her bimonthly infusions take just an hour. "I go in, get it, and feel great," she said.

Follow-up scans show that her tumors are shrinking. "All I look for now is no new masses and stable disease," she laughed. "If it says that, I'm good."

Dawn is deeply religious and credits her faith—and her doctor's relentless optimism—for keeping her alive. "He said, 'You never gave up, so I never will either,'" she recalled.

Now 67, Dawn is committed to paying it forward. She serves as a mentor in Cleveland Clinic's 4th Angel Mentoring Program, supporting other patients with cholangiocarcinoma. "They call me when someone needs help—some people talk to you once, some every day," she said. "They ask about test results, about how I felt, what I went through. It's a privilege to be there for them."

She's also a powerful advocate for federal investment in cancer research. "Every single option I have had was because of clinical trials," she said. "We cannot do any of this without funding. People need hope. And that only comes from research."

To policymakers, she is direct: "We need the money. Period. You want to change the cancer story for millions of people? Fund the science. Fund the trials. Give us something to hold onto."

"You want to change the cancer story for millions of people? Fund the science. Fund the trials."

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

Back to Planning His Life and Future, Thanks to a Breakthrough in Precision Medicine

Alex Hepner
AGE: 25 | OTTAWA, ONTARIO, CANADA

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At 24 years old, Alex Hepner was entering the most exciting stretch of his life. A law student at the University of Ottawa with dreams of working in sports representation, he was healthy, driven, and living on his own near Parliament Hill. But in July 2024, a bout of persistent headaches sent him to the emergency room—a visit that jeopardized his plans for the future.

What began as a routine checkup turned into a life-altering diagnosis. A CT scan showed unexplained tissue swelling in his brain. Though his physician initially reassured Alex that it was not anything too serious, an MRI was scheduled almost immediately—unusually fast, Alex noted in retrospect. That Sunday night, surrounded by his family, Alex received the news: A tumor had been found in the frontal left lobe of his brain, a region critical to language and memory. He was told it was likely a low-grade glioma, but confirmation would require a surgical biopsy. Worse still, surgical removal wasn't an option. The tumor was too embedded in the brain tissue to resect safely.

The news devastated Alex and his family. While he tried to maintain composure, his parents, Julie and Richard, were shaken to their core. "I cried for 80 days straight," Julie recalled. At one point, after misreading the preliminary pathology report, the family feared he had glioblastoma, the most aggressive form of brain cancer. "They thought it was a death sentence," Alex said. "That was the hardest part—watching how much pain they were in." He also had to put his life on hold to address the health situation. "I stopped dreaming about the future before I'd even had the chance to start," Alex said.

The prevailing medical view was to adopt a "watch and wait" approach, monitoring the tumor's progression without intervention. But Alex was fortunate to be referred to Princess Margaret Cancer Centre in Toronto, where neuro-oncologist Dr. Warren P. Mason and his team recommended a more proactive path. Dr. Mason explained that while treatment for low-grade gliomas had traditionally been limited to surgery, radiation, and chemotherapy, a newly approved targeted therapy, vorasidenib, was showing remarkable promise in clinical trials.

Vorasidenib is a brain-penetrant oral therapy that targets altered or mutated IDH proteins, which are commonly found in low-grade gliomas. For Alex, this drug represented a glimmer of hope. But first, he would need a biopsy to confirm the tumor's IDH mutation status. On August 28, 2024, Alex underwent brain surgery to extract a tissue sample. The procedure was terrifying, but it went smoothly.

A few weeks later, Alex received the call he had been hoping for: The biopsy confirmed an *IDH2* gene mutation, qualifying him for vorasidenib. Not only that, but the drug had just been approved by Health Canada. "That was the best phone call of my life," he said.

Alex began treatment on October 28, 2024. He takes the pill every morning on an empty stomach and, so far, has experienced minimal side effects. The main concern—liver enzyme fluctuations—is monitored through regular bloodwork. Early on, he traveled frequently between Ottawa and Toronto for tests, but over time his care team transitioned to monthly remote monitoring. A recent MRI showed no tumor progression, a major milestone in a disease where stability is a victory. "This drug gave me hope. It let me start dreaming again" Alex said.

Dr. Mason, who leads the Gerry and Nancy Pencer Brain Tumour Centre at Princess Margaret Cancer Centre, emphasized how extraordinary this research advance is. "Therapeutic advances for primary brain tumors are few and far between," he said. "Vorasidenib is the most significant advance in two decades. It offers real hope for delaying radiation and chemotherapy—and possibly changing the biology of the disease itself."

For Alex, the drug has been transformative. "It feels like I'm finally living again," he said. He's resumed law school, caught up on missed credits, and secured a summer internship. He's playing sports again, thinking about long-term career goals, and even contemplating relationships, something he had deemed impossible after his diagnosis. "There was a time when I thought I'd just fade away before I had a chance to build a life," he said. "Now, I can actually picture a future."

His parents share that cautious optimism. "It's surreal," Richard said. "He looks and acts like any other 25-year-old, and that's because of this drug."

As someone whose life has been reshaped by science, Alex is now using his legal training to advocate for continued investment in cancer research. "This drug didn't appear out of nowhere. It took 15 years of research. And there are people today who still can't access it," he said. He's raised over $25,000 for Princess Margaret Cancer Centre and recently began working with the drug's manufacturer as a patient consultant.

To policymakers, Alex has a simple message: "Cancer research saves lives—mine is proof. But it doesn't happen without funding. We need to keep investing so that more people get the future I almost lost."

"I'm a walking, talking example of the difference cancer research can make."

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

individuals with NF1 are usually benign, some patients develop malignant tumors, usually in adolescence or adulthood. Plexiform neurofibromas are tumors that arise in cells that form the covering of peripheral nerves. These benign tumors occur in up to 50 percent of patients with NF1 and can cause pain, disability, and disfigurement. They can also go on to become cancerous.

Research has shown that the growth of plexiform tumors in patients with NF1 is fueled by a signaling pathway that includes the MEK family of proteins (612), and in 2020, FDA approved the MEK-targeted therapeutic selumetinib (Koselugo) for treating pediatric patients ages 2 years and older who have NF1-related plexiform neurofibromas that cannot be safely removed surgically. In February 2025, FDA approved a second MEK-targeted therapeutic, mirdametinib (Gomekli), for both adult and pediatric patients 2 years of age and older with NF1 who have symptomatic plexiform neurofibromas not amenable to complete resection. The approval was based on results from a phase II clinical trial showing that 52 percent of pediatric patients and 41 percent of adult patients who received mirdametinib had tumor shrinkage (612).

Mirdametinib offers the first treatment option for adult patients with NF1-related plexiform neurofibromas. Unlike selumetinib, which is only available as capsules, mirdametinib can be taken as a capsule or oral suspension, making it a promising new option for children who may have difficulty swallowing.

In addition to the new molecularly targeted therapeutics discussed above, in the 12 months covered in this report, FDA expanded the use of two previously approved anticancer therapeutics for treatment of childhood cancers. These include belzutifan (Welireg) as the first oral therapy for the treatment of children 12 years and older and adults with pheochromocytomas or paragangliomas—rare tumors that develop in the adrenal glands or nearby nerves—that have spread or are not surgically removable and cabozantinib (Cabometyx) for the treatment of children 12 years and older and adults with pancreatic or non-pancreatic neuroendocrine tumors—tumors in hormone-producing cells inside or outside the pancreas—that have spread or are not surgically removable and have not responded to earlier treatments.

Advances in Treatment With Immunotherapeutics

The immune system is a complex network of cells (called white blood cells; see **Sidebar 39**, p. 129), tissues (e.g., bone marrow), organs (e.g., thymus), and the substances they make (e.g., cytokines) 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 (613). However, as tumor cells acquire new properties during the course of cancer development (see **Understanding the Path to Cancer Development**, p. 29), 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; 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 (614). 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 (615). Cancer immunotherapy refers to any treatment that works by using the immune system to fight cancer. There are various ways in which different immunotherapeutics unleash the immune system to fight cancer (see **Sidebar 40**, p. 130).

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 from attaching to their binding partners on cancer cells and can thereby release the brakes on T cells which trigger previously restrained T cells to attack and destroy cancer cells (616).

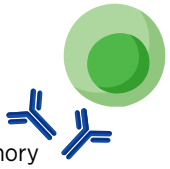
The first ICI approved by FDA was ipilimumab (Yervoy) in 2011, which blocks the checkpoint protein CTLA-4 and was authorized for treating metastatic melanoma (see **Figure 18**, p. 131). This was followed in 2014 by the approval of two additional ICIs—nivolumab (Opdivo) and pembrolizumab (Keytruda)—which 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 brake. 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 third 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

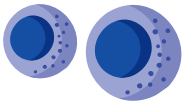
SIDEBAR 39

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.



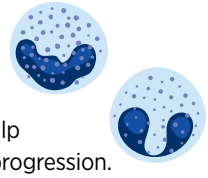
B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help eliminate pathogens as well as help other components of the immune system to function. Some remain as memory B cells to make the same antibody again later, if needed. Understanding of the role of B cells in eliminating 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.



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.

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.

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.

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.

Source: (177).

additional ICIs have been approved since then, relatlimab represents the most recent example of an ICI targeting a novel immune checkpoint pathway.

Since 2011, when the inaugural edition of the *AACR Cancer Progress Report* was published, the use of ICIs has rapidly expanded and these therapeutics are currently considered one of the most exciting approaches to cancer treatment (see **Figure 18**, p. 131 and **Figure 19**, p. 132). 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 (617).

Another clinical trial that monitored advanced melanoma patients 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 (618). 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

SIDEBAR 40

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 more 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) and nogapendekin alfa inbakicept-pmln (Anktiva).

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 tarlatamab-dlle (Imdelltra).

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).

Source: (177).

or combinations like nivolumab plus ipilimumab lead to better survival and fewer side effects over time (618,619).

During the 12 months spanning this report (July 1, 2024 to June 30, 2025), FDA approved two new ICIs—cosibelimab-ipdl (Unloxcyt) and penpulimab-kcqx—and expanded the uses of three previously approved ICIs—durvalumab (Imfinzi), pembrolizumab (Keytruda), and retifanlimab-dlwr (Zynyz)—to include additional cancer types. With these latest approvals the total number of ICIs approved by FDA has reached 15 as of June 30, 2025. These groundbreaking treatments are now approved for treating 22 cancer types as well as any type of solid tumor characterized by the presence of certain molecular characteristics (see **Figure 19**, p. 132).

In December 2024, FDA approved cosibelimab-ipdl, a new PD-L1–targeting ICI, for the treatment of adults with advanced cutaneous squamous cell carcinoma (CSCC) that has spread or that is locally advanced and cannot be treated with surgery or radiation intended to cure the disease.

CSCC is the second most common form of skin cancer in the United States. While existing PD-1–targeted ICIs have improved outcomes for patients with CSCC, treatment options are still limited for patients with advanced or metastatic disease who cannot undergo curative surgery or radiation. Additionally, currently approved ICIs are not effective or well tolerated for all patients, highlighting the need for new options that may be fulfilled by cosibelimab-ipdl.

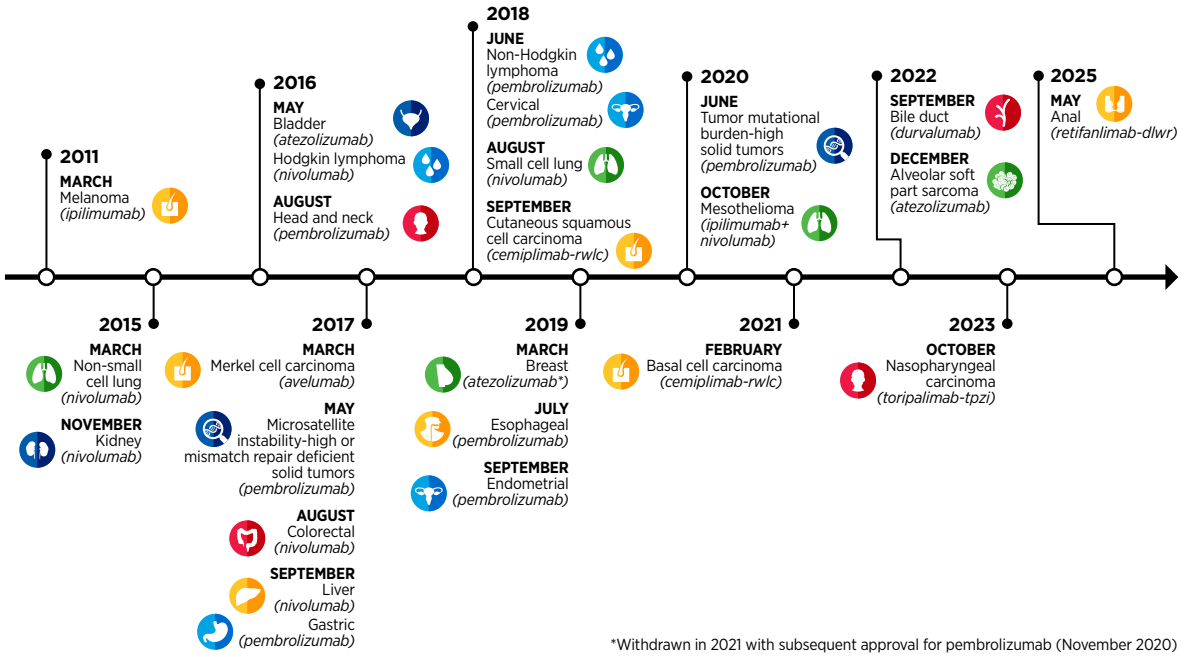
FDA approval was based on results from a phase I clinical trial demonstrating that cosibelimab-ipdl helped shrink tumors in nearly half of the patients (620). These responses were also long-lasting, with many patients continuing to benefit for more than a year. These findings, together with the lower rates of reported adverse events compared to other ICIs, suggest that cosibelimab-ipdl could offer a safer and effective new treatment option for patients with advanced CSCC.

The second new ICI approved by FDA in the 12 months covered in this report is penpulimab-kcqx, a PD-1–targeted ICI. It was approved by FDA, along with chemotherapy, in April 2025 for treating adults with non-keratinizing nasopharyngeal carcinoma (NPC) whose cancer has metastasized or come back and who have not yet received treatment for advanced disease. In addition, penpulimab-kcqx was approved to be used alone for adults whose cancer has worsened after receiving platinum-based chemotherapy and at least one other treatment.

NPC is a rare form of head and neck cancer that starts in the upper part of the throat, behind the nose. The risk of

FIGURE 18

Timeline of First FDA Approvals of Immune Checkpoint Inhibitors for Different Cancer Types



*Withdrawn in 2021 with subsequent approval for pembrolizumab (November 2020)

This timeline illustrates the first US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors (ICIs) for specific cancer types and tumor-agnostic indications from 2011 to 2025. Each entry includes the month and year of approval, the cancer type, and the corresponding ICI name. Icons denote the organ or system affected.

Site-agnostic approvals are also highlighted. Atezolizumab's 2019 breast cancer approval was later withdrawn, with pembrolizumab approved for the same indication in 2020. As of June 30, 2025 immune checkpoint inhibitors were approved for treating 22 cancer types and for treating any type of solid tumor based on the presence of certain biomarkers.

developing NPC is influenced by a combination of factors, including inherited genes, certain viral infections, and environmental or dietary habits. There are different types of NPC. Non-keratinizing NPCs are characterized by the absence of keratin protein in cancerous cells. NPCs are rare in North America and Europe but have a higher incidence in China, North Africa, and India (621).

FDA approval of penpulimab-kcqx was based on results from two clinical studies. In the first trial, a phase III study, patients with metastatic or recurrent NPC who had not received prior treatment for their advanced disease received either penpulimab-kcqx with chemotherapy or chemotherapy alone. Those who received penpulimab-kcqx lived longer without their cancer worsening—about 9.6 months compared to 7 months for those who received only chemotherapy (622). In a second study, a phase II clinical trial, patients whose cancer had progressed after at least two prior treatments received penpulimab-kcqx alone. About 28 percent of patients saw their tumors shrink, and for many, the benefit lasted a long time (623). Unlike other PD-1-targeted ICIs, penpulimab-kcqx was engineered with unique structural features aimed at reducing its adverse effects.

In addition to the two new ICIs discussed above, in the 12 months covered in this report, FDA expanded the use of three previously approved anticancer therapeutics for the treatment of new cancer types. These include retifanlimab-dlwr (Zynyz), approved for patients with advanced anal cancer, the first approval of an ICI for this disease; durvalumab (Imfinzi), approved for certain patients with bladder cancer; and pembrolizumab, approved for patients with advanced mesothelioma, each to be used in combination with standard chemotherapy.

ICIs have yielded extraordinary benefits for many patients. However, they can also have adverse effects, particularly the

FIGURE 19

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 the US Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Since then, over the past decade, 14 additional ICIs have been approved by FDA. In addition, FDA has expanded the number of cancer types for which there is at least one ICI approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of June 30, 2025, at least one ICI was approved for treating 22 cancer types. In addition, there are several cancer types for which a deep selection of ICIs is available as a treatment option.

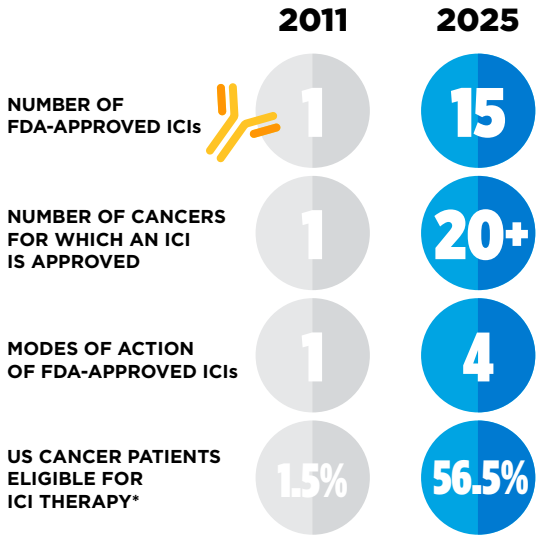
Source: (177).

induction of immune-related adverse events. According to a new analysis, 40 percent of patients receiving ICIs may experience such events, some of which can be life threatening (625). 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 (626,627).

Managing side effects from ICIs in older adults can be especially difficult, particularly when they have comorbidities or are physically frail. Therefore, an urgent medical need is to identify strategies for addressing ICI-related toxicities among older adults (628). Notably, research has shown that although the immune system undergoes complex changes with aging,

15 YEARS PROGRESS AGAINST CANCER

Immune Checkpoint Inhibitors (ICIs)



*Source: (624).

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some cancer patients age 65 and older may still respond well to ICIs, though responses may vary depending on cancer type and study design (629).

While ICIs have been transformative for many cancers, only 20 percent of patients respond to these treatments (624). Identifying cellular and molecular biomarkers that can predict whether ICIs are likely to work in a patient is an area of extensive research investigation. Biomarkers can also help identify patients unlikely to benefit from immune checkpoint therapy, sparing them from unnecessary side effects, high treatment costs, and delays in receiving more effective alternatives.

Using advanced technologies, researchers are exploring several strategies—both before and during ICI treatment—to identify the best biomarkers for predicting response, including measuring cancer-specific proteins (called neoantigens) that help the immune system recognize and attack cancer cells, analyzing the activity of key immune-related genes, and assessing the abundance and spatial distribution of immune cells within tumor microenvironment over time (630–634). One large study in patients with several advanced cancer types showed that five key factors—number of mutations in the tumor, immune cell infiltration of tumors, a molecule that suppresses the immune system, prior treatments, and tumor growth rate—can reliably predict response to immunotherapy and provide a framework for future biomarker research (633).

AI and machine learning are increasingly being used as powerful tools to advance research in this area (see **New Advances in Artificial Intelligence**, p. 194). Recent studies have shown that AI-based algorithms developed using pathologic images, RNA or DNA sequence analyses, or even information from routine clinical tests derived from patients can successfully predict response to ICIs (635–638). As one example, a new AI tool called SCORPIO, which was developed using information from routine blood tests and medical records accurately predicted which cancer patients were likely to benefit from immunotherapy and how long they might live, potentially improving treatment decisions and reducing unnecessary side effects (638).

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.

Increasing evidence is showing that the gut microbiome—bacteria, viruses, and all other microorganisms that live in the digestive system—can impact response to ICIs (639–641). Researchers are currently evaluating how the microbiome enhances the effectiveness of ICIs and exploring strategies to either mimic these effects through therapies or by modifying the microbiome using probiotics, antibiotics, or fecal transplants to make patients more responsive to ICIs.

I'm completely cured!

"Thanks to [my doctor] and the clinical trial using Keytruda for the mutation identified within my tumor, I am alive and thriving. My gratitude and appreciation for the amazing benefits [resulting from] cancer research from so many people's work over years is a major part of everything I do."

Adrienne Skinner

Scan to read Adrienne's story in *AACR Cancer Progress Report 2017*

A New Era in Immune Checkpoint Inhibitor (ICI) Administration

Recent FDA decisions have introduced subcutaneous (under-the-skin) injectable forms of atezolizumab (August 2023) and nivolumab (February 2024), across approved adult, solid tumor indications, offering a more convenient administration strategy than traditional intravenous (IV) infusions.

FEATURE	IV INFUSION	SUBCUTANEOUS INJECTION
Administration time	~30 minutes	~5 minutes
Requires infusion center	Yes	No
Need for port placement	Often	No
Frequency of visits	Regular, scheduled	Potentially less frequent
Patient convenience	Moderate	High

Researchers are also actively testing combinations of different ICIs, pairing ICIs with other forms of immunotherapy, and combining them with other treatment approaches, such as molecularly targeted therapies, to improve effectiveness, safety, and overcoming resistance to cancer treatment.

As one example, two recent clinical trials found that adding a JAK inhibitor, a type of molecularly targeted therapeutic, to ICIs helped improve outcomes for patients with advanced NSCLC and Hodgkin lymphoma, even those who had not responded to previous ICI treatments (642). Researchers showed that the combination worked by reactivating exhausted and inactive immune cells, allowing them to better fight the cancer and leading to stronger and longer-lasting responses. In a separate set of clinical studies, researchers showed that combining ICIs and a type of targeted therapy called angiogenesis inhibitors (see **Sidebar 34**, p. 107) with a standard procedure that involves using a catheter to deliver chemotherapy directly to the liver significantly delayed cancer progression in people with intermediate-stage liver cancer, offering a promising new treatment option (643,644).

ICIs have transformed the clinical care of patients with a diverse array of cancer types, including historically intractable diseases, such as metastatic melanoma, lung cancer, and kidney cancer (see **Figure 19**, p. 132). While their use was initially limited to people with very advanced cancers that were no longer responding to standard treatments, ICIs are now being approved as first-line, or initial, treatments for patients. Researchers are also evaluating how to best integrate the use of ICIs in combination with standard treatments such as surgery, radiation therapy, and/or chemotherapy in patients with early-stage cancers.

One area of extensive research is the use of these therapeutics before initial surgery, known as neoadjuvant treatment (see **Sidebar 32**, p. 101), in people with locally advanced cancers that are largely restricted to the tissue of origin (645). In this regard, a recent clinical trial showed that adding the ICI pembrolizumab before and after standard treatment (surgery and radiation) helped patients with advanced head and neck cancer live longer without the cancer coming back (646). Based on these data, in June 2025, FDA approved pembrolizumab as neoadjuvant treatment and as a combination with radiotherapy, with or without chemotherapy, after surgery for certain patients with head and neck cancers.

In another groundbreaking clinical trial among patients with early-stage cancers that have a specific genetic feature, treatment with the ICI dostarlimab before surgery led to tumor disappearance in most cases, allowing those patients to safely avoid surgery while maintaining excellent outcomes (533). In the study, 103 patients with different types of cancer were treated with dostarlimab. Tumors disappeared in most patients—including all 49 with rectal cancer and many with cancers of the stomach, esophagus, liver, endometrium, urinary tract, and prostate—and after five years, only five experienced a recurrence, all of whom responded well to further treatment.

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.

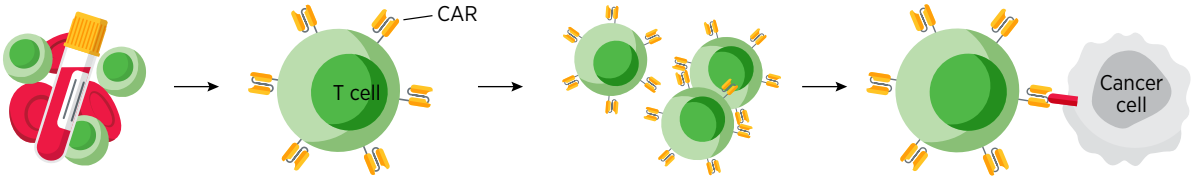
Adoptive cell therapy (ACT), also called cellular immunotherapy, is designed to dramatically increase the number of cancer-killing immune cells a patient has, thereby boosting the immune system's ability to seek and destroy cancer cells (647). While many of the adoptive cell therapies currently in late-stage clinical development, and all that are approved by FDA, utilize patient-derived T cells, 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 41**, p. 135).

SIDEBAR 41

T-cell–based Adoptive Cell Therapy

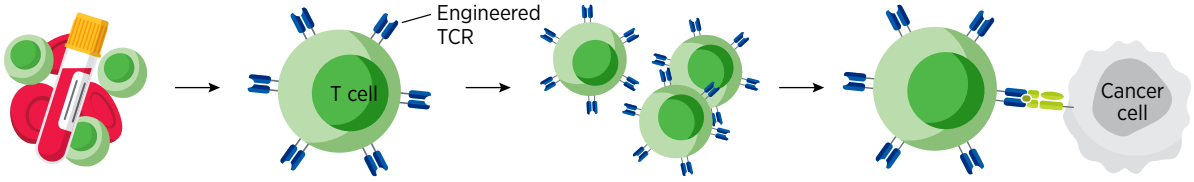
Adoptive T-cell therapy, also called cellular immunotherapy, is a direct infusion of cancer-killing immune T cells, thus dramatically increasing the number of immune cells aiming to seek and destroy cancer cells. It is a complex and multistep medical procedure. During the treatment, T cells are harvested 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.

There are three main types of adoptive T-cell therapy:



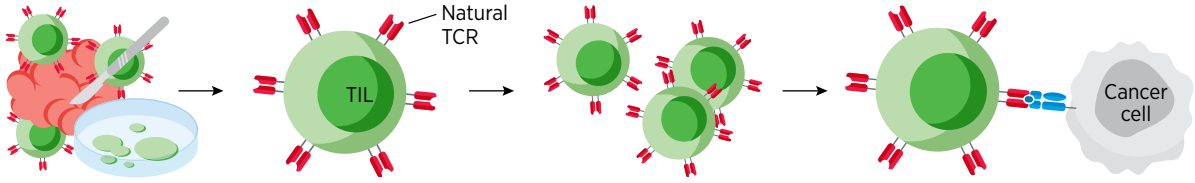
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

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, 2025, 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, 2025, 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, 2025, FDA has approved one TIL therapy, lifileucel (Amtagvi), for patients with advanced melanoma.

Source: (177).

Chimeric antigen receptor (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 (see **A Decade of Progress: Transformative Advances in Blood Cancer**, p. 144). As of June 30, 2025, seven CAR T-cell therapies have been approved by FDA for treating a range of blood cancers.

CAR T-cell therapies can cause significant side effects, some of which, such as cytokine release syndrome (CRS), a condition characterized by excessive immune activation leading to organ toxicity, and immune effector cell–associated neurotoxicity syndrome (ICANS), a neurologic condition leading to confusion, speech difficulties, and seizure, can be potentially life-threatening. Researchers are actively working to identify biomarkers that can predict side effects and to mitigate the significant immune-related toxicities associated with CAR T-cell therapy (648). Strategies under investigation include the development of therapeutic interventions to manage the 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 (648).

Additionally, efforts are underway to develop CAR T-cell therapies against solid tumors, but there are several challenges to 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 immune suppressive nature of the tumor microenvironment. However, there are promising new data showing efficacy of CAR T-cell therapy in a number of solid tumors, including glioblastoma, gastrointestinal cancers, and advanced neuroblastoma (see **Sidebar 42**, p. 137) (649–652). In addition, researchers are exploring whether other types of engineered immune cells, such as CAR macrophages, can effectively treat solid tumors (653).

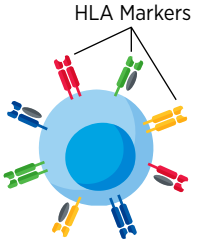
Developing simpler, safer, and faster ways to bring the promise of CAR T-cell therapies to more patients with different types of cancer is an area of ongoing investigation. One area of active research is using T cells collected from healthy donors instead of patients so that these "off-the-shelf" CAR T cells could be readily available for use rather than manufactured for each patient.

Although clinical research has long investigated the effectiveness of the three types of adoptive T-cell therapies, only CAR T-cell therapy had been approved by FDA before 2024. This changed with the approval of the first tumor-infiltrating lymphocytes (TILs), lifileucel (Amtagvi), in February 2024 (discussed in *AACR Cancer Progress Report 2024*), followed by the approval of the first T-cell receptor (TCR) T-cell therapy, afamitresgene autoleucel (Tecelra), in August 2024.

FDA approval of afamitresgene autoleucel, the first-ever TCR T-cell therapy approved for any cancer, marks a major milestone in cancer treatment. Like CAR T cells, TCR T cells are manufactured using a patient's own T cells. However, unlike CAR T cells, which use synthetic receptors to recognize proteins on the surface of cancer cells, TCR T cells use modified versions of natural receptors to identify fragments of cancer-related intracellular proteins that are brought to the cell surface by molecules called human leukocyte antigens (HLAs). HLAs are proteins that are found on the surface of most cells and play a crucial role in helping the immune system detect and destroy cancer cells.

Afamitresgene autoleucel was approved for adults with inoperable or metastatic synovial sarcoma whose tumors test positive for a specific protein called MAGE-A4, and who carry certain HLA types. It is approved for patients who have

What Is Human Leukocyte Antigen (HLA)?



- HLAs are **special proteins found on the surface of most cells** in the body.
- They **help the immune system** tell the difference between one's own healthy cells and foreign invaders like infectious pathogens or cancer.
- **TCR T-cell therapies work only in people with specific HLA types** and depend on HLA proteins to display pieces of cancer-related proteins on the surface so the immune system can recognize and destroy them.
- Therefore, **HLA testing is done before starting treatment** to ensure the therapy will work for the patient.

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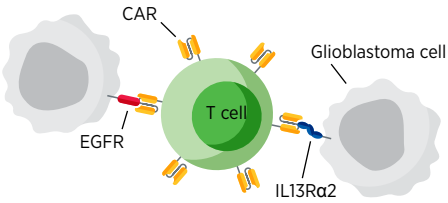
SIDEBAR 42

Targeting Brain Tumors With CAR T Cells

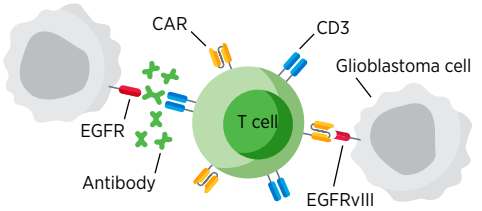
Glioblastoma multiforme (GBM) is an aggressive brain tumor with an average survival of 12 to 18 months. Two recent early-stage clinical studies are providing new hope for patients with this devastating disease.

Study 1



Chimeric antigen receptor (CAR) T cells target two proteins commonly found in brain tumors, EGFR and IL13Rα2.

Study 2

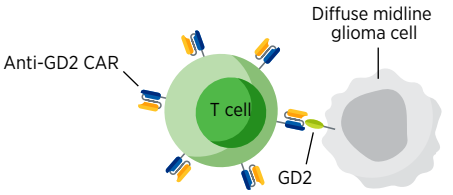


CAR T cells target a mutated form of EGFR known as EGFRvIII and produce a bispecific T-cell–engaging antibody that attaches to EGFR on cancer cells and the protein CD3 on T cells.

In both studies brain tumors shrank in several patients and some experienced long-lasting responses, marking major progress against GBM.

IN ANOTHER CLINICAL TRIAL

A CAR T-cell therapy targeting the cell surface molecule, GD2, significantly shrank tumors and extended survival in children and young adults with a typically fatal brain and spinal cord cancer known as **diffuse midline glioma** (654).



While there are currently no FDA-approved CAR T-cell therapies for brain tumors, these studies offer a promising glimpse into potential future clinical breakthroughs.

already received chemotherapy and have no other curative treatment options.

Synovial sarcoma is a rare and aggressive cancer that usually develops in the soft tissues near joints, such as the arms or legs, and primarily affects young adults like **Quinn Johnsen** (see p. 138). Current treatments include surgery, chemotherapy, and radiation. However, people with advanced or metastatic disease often have limited treatment options and poor outcomes. Only about 8 percent to 15 percent of patients with metastatic cancer live for five years or more after diagnosis (655). Therefore, there is an urgent need for more effective therapies.

Research has shown that synovial sarcoma cells have high levels of the cancer-related protein MAGE-A4, which is the target of the newly approved TCR T cells. HLA proteins display fragments of the MAGE-A4 protein on the surface of tumor cells, helping TCR T cells to recognize and eliminate cancer cells.

FDA approval was based on results from a phase II clinical trial (655) in which over 43 percent of patients with advanced synovial sarcoma who received a single infusion of afamitresgene autoleucel saw their tumors shrink, with some responses lasting more than a year.

CRS was a common immediate side effect seen in 70 percent of patients following treatment with afamitresgene autoleucel. CRS has also been associated with other adoptive T-cell therapies and is characterized by an excessive immune reaction that leads to widespread organ dysfunction that can become life-threatening. While afamitresgene autoleucel–related CRS was usually mild and treatable, experts recommend that this therapy be given at specialized cancer centers with trained health care professionals who are experienced in managing cell-based treatments.

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

continued on page 140

Regaining Normal Life, Thanks to a Novel Personalized Immunotherapy

Quinn Johnsen
AGE: 34 | TORONTO, ONTARIO, CANADA

©2025 AACR/Nor Idoksal

At 31, Quinn Johnsen was a thriving industrial designer in Toronto. He and his partner, now wife, Kate had been together for nearly a decade, sharing a love of city life and new restaurants, with plans for a long future together. But in early 2021, Quinn began feeling unusually exhausted. He went to Toronto Western Hospital, expecting a minor explanation.

Instead, doctors found that Quinn had severe blood loss and that his hemoglobin levels were dangerously low. Further scans revealed a bleeding tumor on the upper side of his stomach. A gastroscopy followed by a biopsy led to the diagnosis of synovial sarcoma, a rare and aggressive cancer typically seen in young adults. Within weeks, Quinn was facing a drastically different future—one defined by blood transfusions, radiation to stop the bleeding, and an urgent treatment plan. "Somebody throws cancer into your life. It is devastating." This was also happening during the tail end of COVID. "While I was at the hospital, it was challenging to see family, making it even more isolating," Quinn said.

As part of his initial treatment plan of radiation, chemotherapy, followed by surgery, Quinn was prescribed a grueling regimen of 6 cycles of chemotherapy starting in March 2021. Each cycle involved four days of in-patient chemo followed by 2 weeks of recovery. He was unable to work and found himself tethered to a rotating schedule of infusions, bloodwork, and side effect management. "It took over everything," Quinn recalled. "I was 31, Kate was 31—we were supposed to be building our lives."

The fourth cycle punctured his stomach lining, leading to two and a half months in the hospital, fed only intravenously, and isolated due to immune suppression. "I could not eat or drink for 2 months. Just waiting, deteriorating, hoping the next thing would work," Quinn said. Despite the immense physical and emotional toll, chemotherapy was very effective. It shrank the tumor significantly and allowed surgeons to proceed with a complex resection, removing part of his stomach.

Quinn had no evidence of cancer for over 2 years after the surgery. However, in June 2024, during a routine scan, a new tumor was discovered in his lower pelvic region—evidence of metastasis. Although it was small, it meant the cancer had returned. Quinn was no longer considered curable by conventional means. He was prescribed an oral chemotherapeutic to mitigate the growth and metastasis.

This is also when Quinn's physician discussed a clinical trial for a novel treatment called afamitresgene autoleucel (afami-cel). Afami-cel is a form of immunotherapy, called TCR T-cell therapy, that re-engineers a patient's own immune cells to recognize and attack cancer cells expressing specific proteins. In Quinn's case, the key was the presence of two rare protein biomarkers, HLA-A02 and MAGE-A4, that made him eligible for the trial. The timing was tight, the trial was closing soon, and samples had to be rushed for genomic validation. But the results came back in time and he made it into the trial.

In September 2024, Quinn underwent a week of chemotherapy to prepare his immune system. Then, over the course of 5 days in the hospital, he received his personalized cell therapy. Unlike chemotherapy, he tolerated the afami-cel well. He did not experience any major side effects. "It was a slow 4 days in the hospital, which is great. Boring in the hospital is wonderful," Quinn said. Over the next few months, each one of the CT scans taken showed a reduction in tumor size. The most recent scans showed the tumor has shrunk by 63 percent.

Quinn's physician now describes his cancer as "stable." "The conversations have changed," Quinn said. "We're talking about how I can get on with my life, not how to brace for what's next. I am able to work, and my friends would agree that my life has kind of returned to as normal as possible from afami-cel treatment."

According to Dr. Albiruni Abdul Razak, Quinn's treating physician, afami-cel is a novel, first-in-class treatment that marks a turning point in sarcoma care. "This is the first time we've had engineered T-cells for solid tumors," he explained. "When we see responses, they can be deep, meaningful, and prolonged." Quinn is living proof. He has returned to full-time work. He and Kate are thinking about the future again.

The broader implications are even more profound. As Dr. Abdul Razak emphasized, rare cancers like synovial sarcoma often lag in research investment and treatment development. Yet, cell therapies like afami-cel demonstrate what's possible when innovation is funded and focused. "While these drugs will be available mostly at specialized centers for now, this is one foot in the door—a real paradigm shift."

Quinn agrees. He believes his experience underscores the need for continued investments in medical research. He emphasized deep gratitude to researchers for developing personalized treatments like afami-cel. He urged the scientific community to keep digging deeper and stressed the importance of continuing to invest in research that addresses both common and uncommon cancers.

"Afami-cel was a silver bullet—built from decades of research. We need to fund more of them."

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

I have been in remission for 17 years, and I am living a fully cancer-free life.

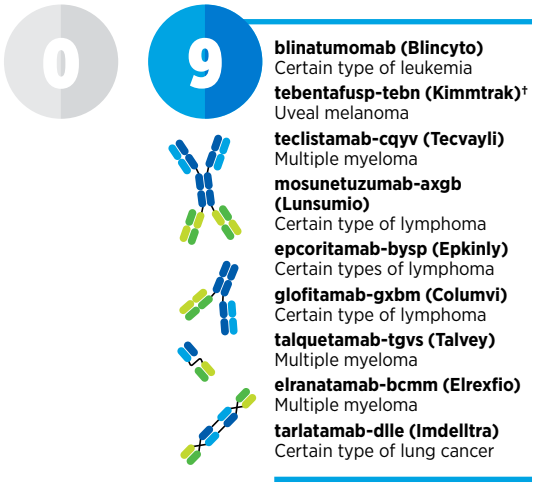
"I would like to say the most sincere thank you to cancer researchers. I owe them my life, and that is a thank you that cannot be expressed in words. Without them, my family would have experienced one of the greatest losses and would have likely been torn by grief. Cancer researchers not only save the lives of those with the disease, but they save the lives of everyone who loves somebody who has or has had cancer."

Elizabeth Buell-Fleming

Scan to read Elizabeth's story in *AACR Cancer Progress Report 2015*

15 YEARS PROGRESS AGAINST CANCER

Rapid Advances in the Development and FDA Approval of Bispecific T-cell Engagers



* As of June 30, 2025.

† Tebentafusp-tebn is a bispecific molecule, not a bispecific antibody. Its one arm is an antibody fragment that attaches to T cells, and the other arm is a T-cell receptor, not an antibody fragment, and is used to recognize and bind to a tumor cell.

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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 acute lymphoblastic leukemia (ALL) called B-cell ALL (see **Redirecting T Cells to Eradicate Blood Cancers**, p. 167) (656). Unprecedented advances in genetic engineering, molecular biology, and immunology over the past decade have led to rapid growth in this innovative new area of cancer medicine. As of June 30, 2025, FDA has approved eight BiTEs for the treatment of cancer (657). Many of these groundbreaking therapeutics are approved for patients with advanced cancer that has returned following several prior treatments or is resistant to therapy.

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 (658).

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 39**, p. 129) (659). 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 so far. The most recent, zolbetuximab-clzb (Vyloy), was approved in October 2024, in combination with chemotherapy, for the initial treatment of adults with locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancers that cannot be removed surgically and that test positive for the protein claudin 18.2 but not HER2. FDA also approved the VENTANA CLDN18 RxDx Assay as a companion diagnostic device to identify patients with gastric or GEJ cancer who are eligible for treatment with zolbetuximab-clzb.

Claudin 18.2 is normally found only in the healthy lining of the stomach, where it is buried within tightly connected cells. In many stomach and gastroesophageal cancers, claudin 18.2 becomes exposed and accessible on the surface of cancer cells, making it easier for antibody-based therapies to find and attack the cancer cells. Hence, claudin 18.2 is a promising new target for cancer treatment.

Zolbetuximab-clzb is the first FDA-approved therapy that targets claudin 18.2, which is now benefiting patients such as **Greg Myers** (see p. 142). By attaching to this protein, zolbetuximab-clzb helps the immune system recognize and kill cancer cells through natural defense mechanisms, including antibody-dependent cellular cytotoxicity.

FDA approval was based on results from two phase III clinical trials. In the first trial, patients who received zolbetuximab-clzb with chemotherapy lived about 10.6 months without their cancer getting worse, compared to 8.7 months for those who received chemotherapy alone (660). In the second trial, patients who received zolbetuximab-clzb with chemotherapy lived about 8.2 months before their cancer worsened, compared to 6.8 months with chemotherapy alone (660).

Advocating for a Strong Future for Stomach Cancer Research

Greg Myers
AGE: 53 | CALIFORNIA CITY, CALIFORNIA

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Greg Myers was 49 years old when he began struggling to swallow his food. It started subtly, just a persistent sensation of food sticking in his throat and worsened over several months. He brushed it off as acid reflux. "I was getting older. I figured that was it," he said.

But his primary care physician wasn't convinced. She prescribed reflux medication but also referred him for an endoscopy. The procedure revealed a mass at the junction between his esophagus and stomach—the gastroesophageal junction. Three weeks later, in July 2021, Greg and his wife received the diagnosis: gastric cancer. "I didn't even know you could live without a stomach. But that's what they told me: we're going to take it out," Greg remembers.

The news was devastating. Greg didn't Google the statistics—but his wife did. "She kept the worst of it from me," he said. At the time, the 5-year survival rate for advanced gastric cancer was dismal.

Greg began treatment at City of Hope in Lancaster, California. Initially, the plan was to perform chemotherapy, then partial stomach removal, followed by more chemo. But during a routine research blood draw for a study at City of Hope, everything changed.

Genetic testing revealed that Greg carried the *CDH1* gene mutation, which confers a high risk for hereditary diffuse gastric cancer in men and women and lobular breast cancer in women. That information altered the course of his treatment—and his family's life.

There would be no partial removal. The surgical team informed him that to eliminate all risk of recurrence, he would need a total gastrectomy—complete removal of the stomach. "We sat in the car afterward just staring at each other," Greg said. "It didn't seem real."

But the most painful part wasn't his own diagnosis. It was what came next. Each of his two children now had a 50 percent chance of inheriting the same gene mutation. "It felt like I had handed them a death sentence. Even though it wasn't my fault, I still felt responsible." Both of Greg's kids tested positive for the *CDH1* mutation. The family didn't hesitate. One after the other, they underwent prophylactic total gastrectomies. In addition, Greg's daughter chose to undergo a double mastectomy and breast reconstruction surgery that same year, given her elevated breast cancer risk.

Between December 2021 and the end of 2022, the Myers household became a rotating recovery ward. Greg, then his son, then his daughter—each had their stomach removed, relearning how to eat and manage life post-surgery. "My wife took care of all of us," he said. "She was the one who kept it together."

The initial chemotherapy, called the FLOT regimen, came with side effects: cold sensitivity, painful neuropathy in his hands and feet, and fatigue. But it was manageable. Later, when his cancer returned in early 2023, Greg underwent HIPEC (hyperthermic intraperitoneal chemotherapy)—a physically grueling procedure that delivered chemotherapy directly into his abdomen.

It took a toll. Greg now lives with extensive internal scar tissue, making it difficult to stand upright or move comfortably. He wears an ostomy bag and receives daily total parenteral nutrition (TPN) through a PICC (peripherally inserted central catheter) line, sleeping connected to an IV for 16 hours a day. On top of that, he still receives zolbetuximab-clzb, an investigational therapy. So far, it's been relatively gentle compared to prior treatments—mostly causing fatigue and occasional nausea. "Some weekends I just sleep. But I'm lucky. I know people who've had it worse."

Zolbetuximab-clzb was offered after the discovery of a new nodule while his care team evaluated removal options. Traditional ablation posed too much risk to his colon, so his doctors used a novel technique—pulsed electric field therapy—to target the tumor without surgical damage. Greg awaits scan results to see if it worked.

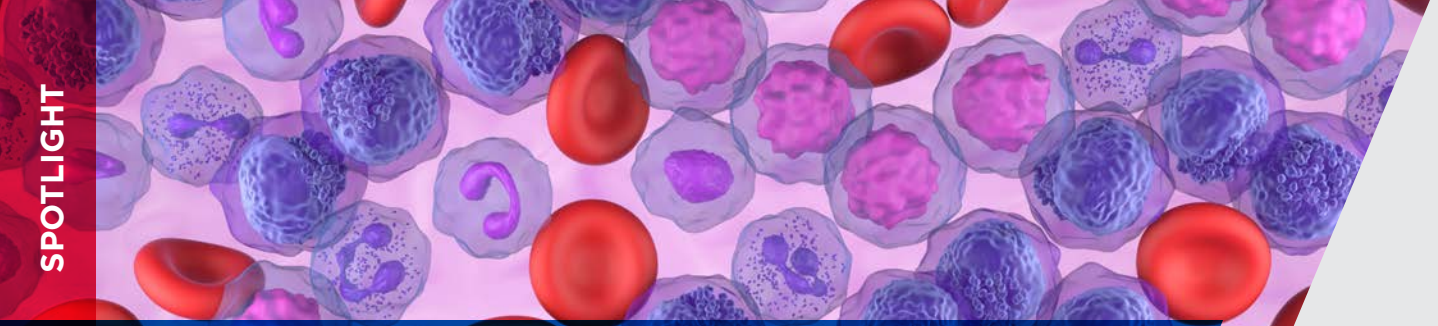
Despite the challenges, Greg remains focused on advocacy. In 2023, Greg traveled to Washington, DC, to share his story with members of Congress and push for increased funding for stomach cancer research, an area he says is critically underfunded relative to its lethality. "We're not asking for miracles. We're asking for a fighting chance," said Greg.

His message to Congress is straightforward: Gastric cancer doesn't get enough attention or resources. "The treatment hasn't changed in years. We're just trying to stay alive long enough for the next drug to come out," he said. "And that only happens with research and funding." Greg is also urging the public to advocate for more early detection tools for stomach cancer. "Right now, most people are diagnosed late. They walk into a doctor's office with symptoms and get told it's acid reflux—just like I was. By the time it's caught, it's stage III or IV. We need endoscopies, not guesses."

Even now, Greg's battle isn't over. He faces mobility limitations, extreme fatigue, and nutritional hurdles. But his kids are thriving and active—and they credit their father for showing them how to lead with strength. "You'd never know they don't have stomachs. They're out there living full lives," he said.

"I'm still here. I'm still fighting. And I'll keep going as long as there's another option to try."

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



A Decade of Progress: Transformative Advances in Blood Cancer

IN THIS SECTION, YOU WILL LEARN:

- Blood cancers, or hematologic malignancies, make up a large group of cancers that originate from blood-forming tissues.
- Tremendous progress against blood cancers in the past decade has significantly decreased blood cancer–related deaths, improved survival rates, and helped survivors live fuller lives.
- Advances in understanding blood cancers have led the revolution in precision cancer medicine. Over the past decade, the US Food and Administration (FDA) approved 29 new molecularly targeted therapies and 21 new immunotherapeutics to treat various types of hematologic malignancies.
- Progress against blood cancers has often accelerated progress against solid tumors as well as against diseases beyond cancer.
- Despite the progress, certain populations within the United States, as well as certain regions around the globe, experience a disproportionate burden of blood cancers, primarily due to lack of access to breakthrough treatments and lack of infrastructure.
- Knowledge gleaned from decades of research is helping inform strategies to intercept and eliminate cells that may progress into blood cancers.

In adults, normal blood formation takes place in the bone marrow, which is found inside certain bones, such as the hips, ribs, and spine (see **Figure 20**, p. 145). Blood cancers, also called hematologic malignancies, are a large group of cancers that arise when normal blood formation goes awry and results in abnormal, immature cells called blasts.

Blood cancer cells are often incapable of performing normal functions, such as defending the body against pathogens, dividing in a controlled manner, or eliminating abnormal or dead cells from the body (see **Sidebar 39**, p. 129). Blood cancer cells also acquire properties, such as the ability to infiltrate vital organs or to evade the immune system, that make them aggressive. Blood cancers are broadly classified based on the tissue or cells from which they originate and how fast they grow (see **Sidebar 43**, p. 146).

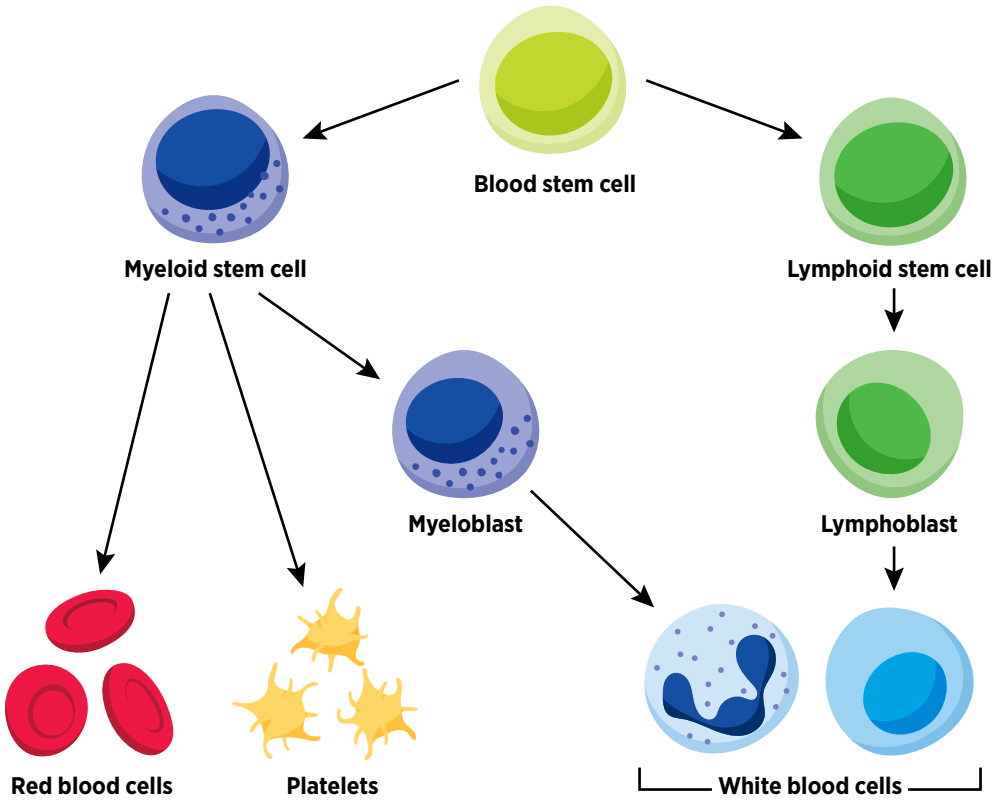
The State of Blood Cancers in 2025

Over the past few decades, research discoveries and technological advances have fueled tremendous progress against blood cancers. As an example, mortality rates for non-Hodgkin lymphoma (NHL)—the most common type of blood cancer in the United States (see **Table 7**, p. 147)—have declined by 47 percent between 1997 and 2023 (4), largely because of advances in precision therapies driven by research. As of January 1, 2025, 879,290 individuals with an NHL diagnosis were living in the United States (9).

Despite major advances, blood cancers pose a significant public health challenge, both in the United States and around the

FIGURE 20

Blood Formation in Adults



In bone marrow, blood stem cells, also called hematopoietic stem cells, divide and commit to one of two major branches. The myeloid branch gives rise to red blood cells that transport oxygen, platelets that orchestrate clotting, and neutrophils, basophils, and eosinophils that destroy microbes. The lymphoid branch generates B and T cells that constitute the immune system and are responsible for coordinated immune responses. Disruption of this intricate process anywhere along the process of blood formation can lead to blood cancers, such as leukemia, and other blood disorders, such as anemia.

globe. In 2025 in the United States, blood cancers will account for about 9 percent of all cancer cases and deaths. Globally, blood cancers accounted for 6.6 percent of total cancer cases and 7.2 percent of total cancer-related deaths in 2022, the most recent year for which such data are available (9).

Leukemias

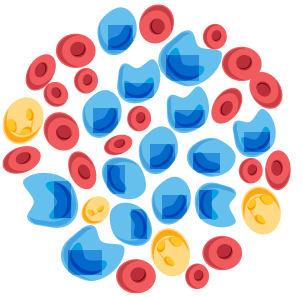
Leukemias are blood cancers that start in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the bloodstream. According to 2025 estimates, 66,890 new cases of leukemia and 23,540 deaths from the disease will occur in the United States (see **Table 7**, p. 147). Leukemia is the most common cancer in children (ages 0 to 14) and adolescents (ages 15 to 19) (6). Depending on the cell of origin and how fast cancer grows (see **Sidebar 43**, p. 146), there are four major categories of leukemias.

Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) affect the myeloid lineage of blood cells (see **Figure 20**, p. 145). AML is a fast-growing cancer in which myeloid progenitor cells—cells capable of giving rise to all cell types in the myeloid lineage—lose their ability to mature and overcrowd the bone marrow, sometimes spilling into organs, such as gums or skin. AML is the second most common leukemia among adults age 20 years and older, accounting for 31 percent of all leukemia cases in this age group. AML mortality rates across age groups have declined every year from 1.9 percent in 2013 to 2.8 percent in 2022 (6); however, the 5-year survival remains at 33 percent (4).

SIDEBAR 43

Types of Blood Cancers

The term blood cancer covers a wide range of diseases that differ in the cells from which they arise, how they affect the body, and how quickly they progress. The most recent World Health Organization classification recognizes hundreds of subtypes of blood cancers, a list that is continuously evolving as our understanding of the biology of blood cancers expands (661).



Below is an at-a-glance summary of how blood cancers are broadly classified. Each of the indicated blood cancer types has numerous subtypes, depending on where the cancer develops along the maturation of the blood and immune system, the type of blood cell or immune cell that gives rise to cancer, or the type of genetic alteration that causes the cancer.

Based on the site where blood cancers originate

CANCER TYPE	WHERE IT STARTS	WHAT IT AFFECTS	COMMON SYMPTOMS
Leukemias	Immature blood stem cells and/or progenitor cells that give rise to the myeloid or lymphoid lineages	Bone marrow and blood	Fatigue, frequent infections, easy bruising
Lymphomas	Immature blood stem cells and/or progenitor cells that give rise to the lymphoid lineage	Lymph nodes, spleen, immune system	Painless swelling, fevers, night sweats
Plasma cell cancers (e.g., multiple myeloma)	Antibody-producing plasma cells	Bones, kidneys, blood proteins	Bone pain, anemia, kidney problems

Based on how fast the disease progresses

CLASSIFICATION	SPEED OF PROGRESSION	TYPICAL CELL TYPE	URGENCY OF TREATMENT	EXAMPLES
Acute	Rapid onset; days to weeks	Very immature “blast” cells	Requires immediate treatment	AML, ALL
Chronic	Slow-growing; months to years	More mature or partially mature cells	Often monitored first; does not require immediate treatment	CML, CLL

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia.

CML is a slow-growing cancer, which usually begins when a stem cell in the bone marrow acquires a genetic alteration known as the Philadelphia chromosome. The Philadelphia chromosome, in which pieces of chromosomes 9 and 22 break off and trade places with each other, produces the abnormal BCR-ABL1 protein that drives uncontrolled growth of cancer cells. CML usually occurs in older adults and rarely occurs in children. In 2025, nearly 10,000 new cases of CML are estimated to be diagnosed in the United States (see **Table 7**, p. 147). While the overall CML incidence has increased slowly since the early 2000s, the mortality from the disease has halved (4), with 70 percent of CML patients age 20 and older living 5 years or more following their diagnosis (6). The incredible progress against the disease has been made possible by decades of

TABLE 7

Most Common Blood Cancers: Estimated Number of New Cases and Deaths in the United States and Globally in 2025

	United States		Global	
	NEW CASES	DEATHS	NEW CASES	DEATHS
Most common blood cancers combined	**192,070**	**56,110**	**1,402,520**	**744,840**
Leukemia	**66,890**	**23,540**	**515,150**	**323,560**
Acute myeloid leukemia	22,010	11,090	–	–
Chronic myeloid leukemia	9,560	1,290	–	–
Acute lymphocytic leukemia	6,100	1,400	–	–
Chronic lymphocytic leukemia	23,690	4,460	–	–
Other leukemia	5,530	5,300	–	–
Lymphoma	**89,250**	**20,540**	**685,470**	**291,110**
Hodgkin lymphoma	8,720	1,150	86,600	24,040
Non-Hodgkin lymphoma	80,530	19,390	598,870	267,070
Myeloma	**36,110**	**12,030**	**201,900**	**130,170**

Sources: (6,30).

Overall just glad to be alive and able to enjoy time with my kids and wife.

"Perspective, how it's changed. It's helped me be a better father (I hope), a husband, a coach, and a friend. The most important lesson I think I learned was how to tell the difference between a problem and an inconvenience. Once I had perspective, things were always easier to handle."

Hans Loland

Scan to read Hans' story in *AACR Cancer Progress Report 2013*

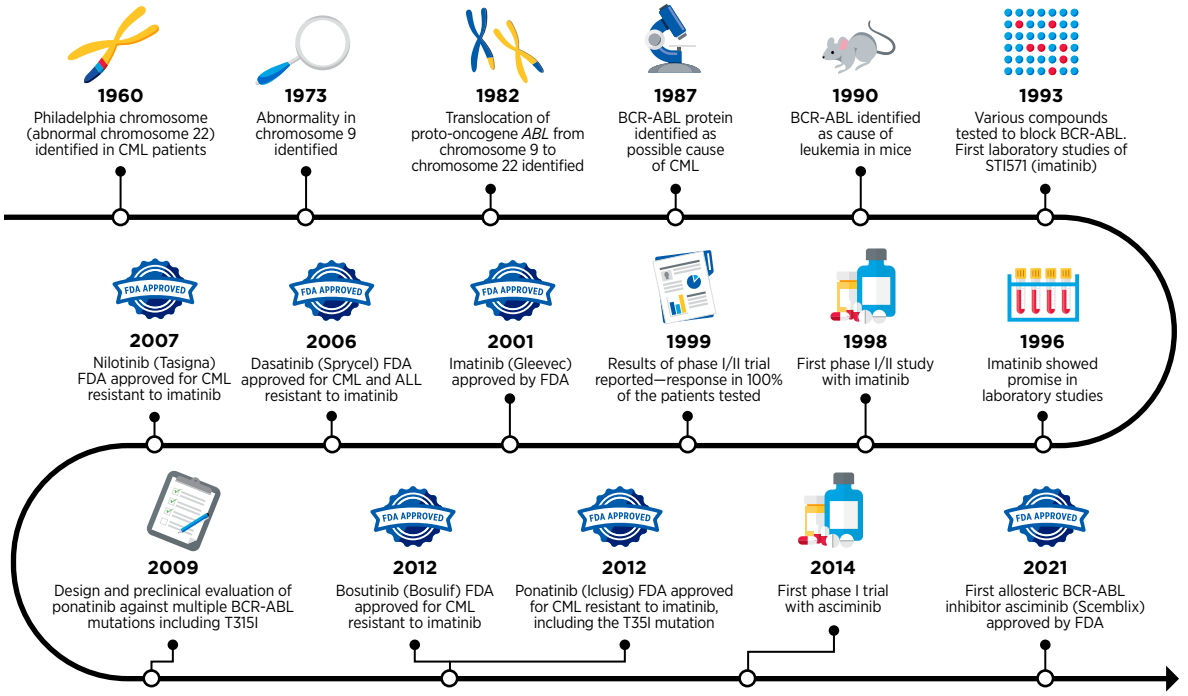
research that led to understanding the biological underpinning of CML as well as FDA approval of several molecularly targeted therapies, significantly expanding treatment options for patients (see **Figure 21**, p. 148).

Acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL) affect the lymphoid lineage of blood cells (see **Figure 20**, p. 145). ALL is characterized by the rapid accumulation—mostly in the bone marrow but sometimes in the chest or brain—of immature lymphocytes, white blood cells that give rise to mature B and T immune cells. ALL is the most common type of leukemia in children and adolescents (ages 0 to 19) (6), and thanks to research-driven advances in understanding the disease as well as the development of effective treatments, the 5-year relative survival rate is 90 percent in this age group (6).

CLL is a slow-growing cancer that affects more mature antibody-producing B cells that accumulate in blood, bone marrow, and lymph nodes. In the modern classification of leukemias, CLL and small lymphocytic lymphoma (SLL), a type of NHL, are essentially the same disease but differ in where the cancer cells are primarily found. CLL cells are mostly in the blood and bone marrow while SLL cells are mainly in the lymph nodes and lymphatic tissues. CLL/SLL is the most common leukemia among adults ages 20 and older in the United States, accounting for about 38 percent of leukemia cases in this age group (see **Table 7**, p. 147). The treatment landscape for patients with CLL/SLL has dramatically changed since the approval of the first molecularly targeted therapeutic, ibrutinib (Imbruvica), against the disease in 2014 (579). The 5-year survival rate for CLL/SLL is 92 percent for those diagnosed in 2017, the most recent data year (4).

FIGURE 21

The Pathway to Progress Against Chronic Myelogenous Leukemia



Development of one of the very first molecularly targeted therapy approved by the US Food and Drug Administration (FDA)—imatinib (Gleevec)—was the culmination of groundbreaking discoveries over decades of research, largely supported by federal funding. The story began in 1960, when a multi-institutional collaborative team of researchers noted that the majority of patients with chronic myeloid leukemia (CML) had an abnormal chromosome 22, which was called the Philadelphia chromosome (so named because it was discovered at research institutes located in Philadelphia, Pennsylvania). In 1973, the abnormal chromosome 9 was discovered and, in 1980, researchers found that the two chromosomes traded pieces to generate an entirely new protein, BCR-ABL. Further research revealed that CML is caused by the BCR-ABL activity, leading to the development of many drugs that shut off the BCR-ABL functions by blocking the most active sites within the protein.

Clinical trials for many of the drugs, including imatinib, began in 1998, resulting in FDA approval in 2001 of imatinib for treating Philadelphia chromosome–positive CML. Subsequently, identification of imatinib-resistant patients led to the development and FDA approval of dasatinib (Sprycel) in 2006, nilotinib (Tasignia) in 2007, and bosutinib (Bosulif) in 2012. However, none of these drugs were effective against the T315I BCR-ABL mutation. In late 2012, FDA approved ponatinib (Iclusig) for treating T315I-mutant CML. Since its approval, ponatinib has benefited many patients; however, its success in treating patients whose CML cells have acquired the highly resistant T315I BCR-ABL mutation has been greatly varied. In October 2021, FDA approved asciminib (Scemblix), the first BCR-ABL inhibitor that binds to a different active site of the protein than any of the drugs indicated above, and persistently blocks the activity of the mutated form of BCR-ABL. In October 2024, FDA approved asciminib for adults with Philadelphia chromosome–positive CML in the chronic phase.

NON-HODGKIN LYMPHOMA
IS ESTIMATED TO ACCOUNT FOR
41% OF ALL NEW CASES AND 32% OF ALL DEATHS
FROM BLOOD CANCERS IN 2025 IN THE UNITED STATES

Source: (6).

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Lymphomas

Lymphomas are blood cancers that begin in lymphocytes, which are a type of white blood cell that helps fight infection (see **Figure 20**, p. 145). Lymphomas are the most common type of blood cancers in the United States, with an estimated 89,070 new cases and 20,540 deaths from the disease in 2025 (see **Table 7**, p. 147). Lymphomas are broadly grouped into Hodgkin lymphoma (HL) and NHL, based on how the cancer cells look under a microscope and what mutations drive them. From 2012 to 2021, the overall incidence of both types of lymphoma has steadily declined (6).

HL is marked by the presence of cells called Reed-Sternberg or Hodgkin cells, which are large, abnormal lymphocytes that may contain more than one nucleus. The number of these cells increases as the disease progresses. HL more commonly affects young adults and will account for about 10 percent of all lymphoma cases diagnosed in 2025 (see **Table 7**, p. 147). Between 2013 and 2022, the HL death rate declined by 2.5 percent every year. For those diagnosed in 2017, the overall 5-year survival rate is more than 98 percent for children (ages 0 to 14) and adolescents (ages 15 to 19) (4). As of January 1, 2025, 235,110 individuals with an HL diagnosis were living in the United States (9).

NHL is a more diverse group of over 80 distinct cancers, some slow-growing and others very aggressive. NHL is the most common type of blood cancer in the United States and globally (see **Table 7**, p. 147). NHL can occur at any age and can be formed from either B cells, such as diffuse large B-cell lymphoma (DLBCL), or T cells, such as anaplastic large cell lymphoma (ALCL). Unlike HL, for which the overall risk peaks during adolescence and early adulthood, the overall risk of developing NHL increases with age. Five-year survival rates for those diagnosed with NHL between 2015 and 2021 are 74 percent (4); however, these rates vary widely across the subtypes (see **Table 8**, p. 149).

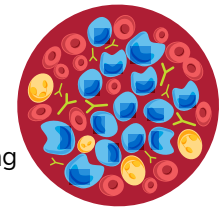
Multiple Myeloma

Multiple myeloma is a cancer of plasma cells, which are responsible for producing antibodies. In this disease, cancerous plasma cells crowd the bone marrow and release abnormal antibodies (M proteins) that can damage the kidneys, weaken bones, and cause anemia and high calcium levels. Multiple myeloma often starts quietly, first appearing as a precancerous state like monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma, which carries risk but does not cause symptoms (see **Intercepting Precancerous Conditions in Blood Cancers**, p. 171).

According to the most recent estimates, multiple myeloma will account for 18 percent of all blood cancer cases and 20 percent of all deaths from blood cancers in the United States in 2025 (see **Table 7**, p. 147). The 5-year relative survival rate is 64 percent for all stages but varies significantly based on the stage at which the cancer is detected. For example, the 5-year survival rate is just 62 percent for those diagnosed when the cancer has metastasized—about 96 percent of all multiple myeloma cases—compared to 81 percent for those diagnosed when the cancer is still confined to the primary site—about 3 percent of all myeloma cases (4). As of 2022, the most recent year for which such data are available, an estimated 192,000 people in the United States were living with multiple myeloma (4).

There are also several hematologic malignancies that can progress into one of the main subtypes discussed above. As

From 1999 to 2020 in the United States, **multiple myeloma incidence rose by 20%, while mortality decreased by 9%**, underscoring advances in treatment and disease management.



Source: (663).

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TABLE 8

Survival Rates of the Most Common Subtypes of non-Hodgkin Lymphoma

Subtype	% Survival Rate*
Diffuse large B-cell lymphoma	66.5
Follicular lymphoma	90.5
Mantle cell lymphoma	72.9
Marginal zone lymphoma	91.3
T-cell lymphoma	72.1

* Indicated rates represent 2-year observed survival for those diagnosed with the shown subtype during 2015–2019.

Source: (662).

one example, myelodysplastic syndromes (MDS) are a group of bone marrow disorders in which immature blood cells fail to develop properly, leading to low counts of one or more types of blood cells. These disorders are often caused by mutations acquired during a person's lifetime. MDS can remain stable or progress to leukemia, and intervention varies from surveillance to intensive treatment.

Blood Cancers: An Ongoing Challenge

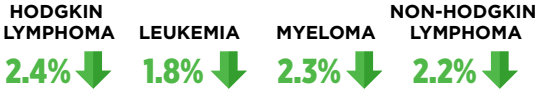
Incidence and mortality rates for all blood cancers combined have been steadily declining in recent years, but trends vary by age, sex, race, and blood cancer subtype. For example, the overall incidence of HL decreased by 1.4 percent every year between 2013 and 2022, but the incidence of CML rose by 1 percent annually during the same time frame.

Another example of varying trends is the multiple myeloma incidence rates by sex. Between 2013 and 2022, the multiple myeloma incidence rose at more than twice the rate among females (3.2 percent every year) compared to males (1.4 percent every year) (4). Similarly, while 5-year relative survival has increased across subtypes of blood cancer since 2000 (4), survival gains greatly differ among different subtypes of blood cancers. As one example, 5-year relative survival spans from 89 percent in HL to just 33 percent in AML (4).

Global Burden of Blood Cancers

Over the past three decades, the global burden of hematologic malignancies has evolved considerably, with both encouraging progress and persistent challenges. Leukemia continues to account for the leading cause of mortality from hematologic malignancies; in 2022, leukemia was the 13th most frequently diagnosed and the 10th leading cause of cancer deaths globally. However, there are encouraging long-term trends. From 1990 to 2019, leukemia mortality rates declined significantly, with the steepest decreases seen in regions with high sociodemographic index (SDI)—a composite measure of a country's development, based on income per capita, educational attainment, and fertility rate (664). Among leukemia subtypes, CML has seen the largest mortality declines, especially in high-SDI countries (664). In contrast, low-SDI regions bear a disproportionate mortality burden despite lower incidence (664).

Annual Decline in Mortality in the United States (2014–2023)



Source: (4).

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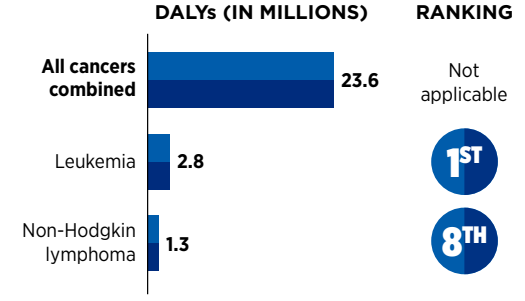
Leading Causes of Disability-adjusted Life-Years (DALYs)* Globally in Adolescents and Young Adults, Ages 15–39 (2019)



* DALY—a measure of overall disease burden that combines years of life lost due to premature death and years lived with disability.

Source: (665).

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In 2022, NHL was the most common hematologic malignancy and the 10th most diagnosed and 11th leading cause of cancer deaths globally (56). Rates of mortality and disability-adjusted life-years (DALY)—a measure of overall disease burden that combines years of life lost due to premature death and years lived with disability—for NHL declined from 1999 to 2021, particularly in high-SDI regions (such as North America) (666). HL has also shown global declines in both incidence and mortality, with the most progress observed in high-SDI regions (666). These encouraging global trends are also observed in childhood NHL; from 1990 to 2021, rates of mortality and DALY for childhood NHL have each declined by 40 percent (667).

Multiple myeloma contributed to about 1 percent of all cancer diagnoses and cancer-related deaths globally in 2022 (56). During the period from 1990 to 2019, the incidence of multiple myeloma increased across all five SDI regions, with the largest estimated annual change of 0.8 percent in middle-SDI regions (664).

Despite major advances in the treatment of blood cancers, access to breakthrough therapies like molecularly targeted therapies and immunotherapeutics, such as CAR T-cell therapy, and hematopoietic stem cell transplants remains highly uneven across the globe. Many low- and middle-income

countries face critical shortages in infrastructure that make it difficult to support the necessary specialists trained in precision diagnostics, as well as to provide supportive care needed by patients and their caregivers, further exacerbating disparities in outcomes (668,669). Addressing these global inequities will require sustained investment in workforce training, technology transfer, and regionally adapted care delivery models.

Disparities in the Burden of Blood Cancers in the United States

Despite tremendous progress in recent years, disparities in the burden of blood cancers continue to span the entire cancer research and care continuum. As an example, in 2023, the most recent year for which data are available, the HL incidence rate was the same among Black and White individuals under the age of 50. However, from 2019 to 2023, HL mortality in this age group declined at nearly four times the rate among White individuals (9.8 percent every year) compared to Black individuals (2.6 percent every year) (4). Examples of such disparities exist at many levels (see **Sidebar 44**, p. 152) and are influenced by biology, lived experiences, access to health care systems, and broader social drivers of health (668).

Certain genetic variants linked with ancestry—such as those in *GATA3*, *IKZF1*, and *SETD2* genes—are more common in Black and Hispanic populations and influence not only the likelihood of developing blood cancers but also how well patients respond to treatment (679–683). These biological differences are often compounded by structural barriers. People from medically underserved communities are more likely to live in areas with poor health care access, face higher rates of comorbidities, and be diagnosed at more advanced stages. In many cases, they mistrust the medical system, and also face lower enrollment in clinical trials, as well as longer delays to treatment (12). New policies and national initiatives must be coupled with sustained investment in community trust, culturally tailored care, and workforce diversity if we are to have a meaningful impact on reducing disparities (668).

Growing evidence indicates that access to health care plays an important role in reducing the burden of the disease across population groups. As one example, when Black and White patients with multiple myeloma received comparable treatment and had similar socioeconomic status, overall health, and the stage at which the disease was diagnosed, disparities in survival were effectively eliminated (684). In fact, Black patients had a 4.6 percent higher 5-year survival rate than White patients within the matched cohort (684). Findings of this study reaffirm an increasingly evident view that differences in health outcomes for patients with cancer are largely attributable to differences in access and delivery of care (12). Addressing disparities requires a reimagining of how care is delivered, who identifies and shapes research priorities, and how social drivers of health—such as income inequality and educational access—are integrated into cancer control and care strategies.

Unique Biology of Blood Cancers

Unlike solid tumors that grow as distinct masses, blood cancers arise from a dynamic system of blood and immune cells. The fluid nature of blood and its continuous renewal via hematopoietic stem cells—capable of giving rise to the entire blood and immune system—and progenitor cells—capable of giving rise to mature myeloid or lymphoid cells—creates a unique biological landscape (685). As a result, leukemias, lymphomas, and multiple myeloma often manifest not in one organ but throughout the circulatory or lymphatic system (see **Sidebar 45**, p. 153, and **Circulatory and Immune Systems**, p. 41).

Genetic and epigenetic disruptions in blood cancers frequently alter the functions of genes involved in the regulation of cell growth, identity, and chromosome structure. In myeloid leukemias, mutations in genes, such as *DNMT3A*, *TET2*, *RUNX1*, *NPM1*, and *IDH1/2*, are often early events contributing to cancer development, as well as to treatment resistance (686,687). For example, mutations in the *DNMT3A* gene alone occur in about 20 percent to 30 percent of AML cases and are associated with an altered epigenome (688). These mutations often co-occur and cooperate with mutations in cellular processes that regulate cell proliferation, such as mutations in the *FLT3* gene, to drive leukemia (689).

Unlike solid tumors, blood cancers carry fewer overall somatic mutations (see **Genetic Alterations**, p. 34), but a higher frequency of mutations in proteins, such as EZH2 and cohesin, that are involved in epigenetic regulation of cell functions (690,691). Similarly, mutations in genes—such as *GATA2* and *CEBPA* that are critical for normal development and maturation of immune cells—lead to the development of B-cell lymphomas and multiple myeloma, as well as confer treatment resistance in these cancer types (692). Inherited or germline mutations (see **Figure 6**, p. 36) play a substantial role in blood cancer development, with approximately 5 percent to 10 percent of myeloid malignancy cases harboring pathogenic variants in genes, such as *RUNX1*, *GATA2*, and *CEBPA* (693). These variants often increase a person's lifetime risk for conditions such as MDS and AML. As our understanding of inherited risk genes deepens, genetic testing, especially at diagnosis, is becoming essential for tailoring treatment and guiding family risk management strategies (694).

Chromosomal rearrangements are structural genetic alterations in which two chromosomes exchange genetic material to make a new gene that can lead to the development of cancer by a variety of mechanisms (see **Sidebar 8**, p. 35 and **Figure 22**, p. 154) (695). Blood cancers are characterized by a higher frequency of

SIDEBAR 44

Disparities Across the Continuum of Blood Cancer Research and Care

Despite remarkable treatment gains, outcome gaps persist along racial, ethnic, socioeconomic, and geographic lines. Below are examples from recent studies, underscoring the persistent gaps in blood cancer burden.

Incidence/ Mortality	**TWICE AS HIGH** In 2020, mortality rate for Black patients with MM was twice as high as White patients (670). **60% HIGHER** NHOPI patients with NHL were 60 percent more likely to die from any cause compared to White patients with NHL (15). **MORE THAN DOUBLE** Lesbian women have more than double the likelihood of being diagnosed with NHL compared to straight women (17). **77% MORE** HL was 77 percent more prevalent among residents of rural areas compared to residents of urban areas in the Midwest region (671).
Social Drivers of Health	**47% LOWER** Patients with HL living in areas with the highest SVI—a measure of how likely a community is to face worse outcomes during a crisis—had 47 percent lower average survival compared to those living in lowest-SVI areas (89.5 vs. 47.3 months) (672).
Ancestry	**MORE THAN TWICE AS LIKELY** Patients of African ancestry were more than twice as likely to present with a high-risk subtype of T-ALL compared to those of European ancestry (673).
Treatment/ Clinical Trials	**40% LESS LIKELY** AYA women with HL were 40 percent less likely to receive radiation compared to AYA men with HL (674). **72% UNDERREPRESENTED** Hispanic patients with AML were 72 percent underrepresented in randomized clinical trials compared to the AML incidence rates in the population (675). **70% LESS LIKELY** Black patients with NHL and MM were 70 percent less likely to receive CAR T-cell therapy, a cutting-edge immunotherapy that has transformed outcomes for certain blood cancers, compared to White patients (676). **ONLY 12%** Only 12 percent of Medicaid enrollees diagnosed with MM received stem cell transplants within the first year of Medicaid enrollment (677).
Survivorship	**32% LESS** Among individuals with any blood cancer diagnosis, Black patients had 32 percent lower use of palliative care compared to White patients (678).

AML, acute myeloid leukemia; AYA, adolescent and young adults (ages 15–39); CAR T-cell therapy, chimeric antigen receptor T-cell therapy; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NHOPI, Native Hawaiian or Other Pacific Islander; SVI, social vulnerability index; T-ALL, T-cell acute lymphoblastic leukemia.

SIDEBAR 45

Key Differences Between Blood Cancers and Solid Tumors

Blood cancers and solid tumors differ in where they arise, how they spread, and how they are classified and treated. Below are key biological and clinical distinctions between the two groups.

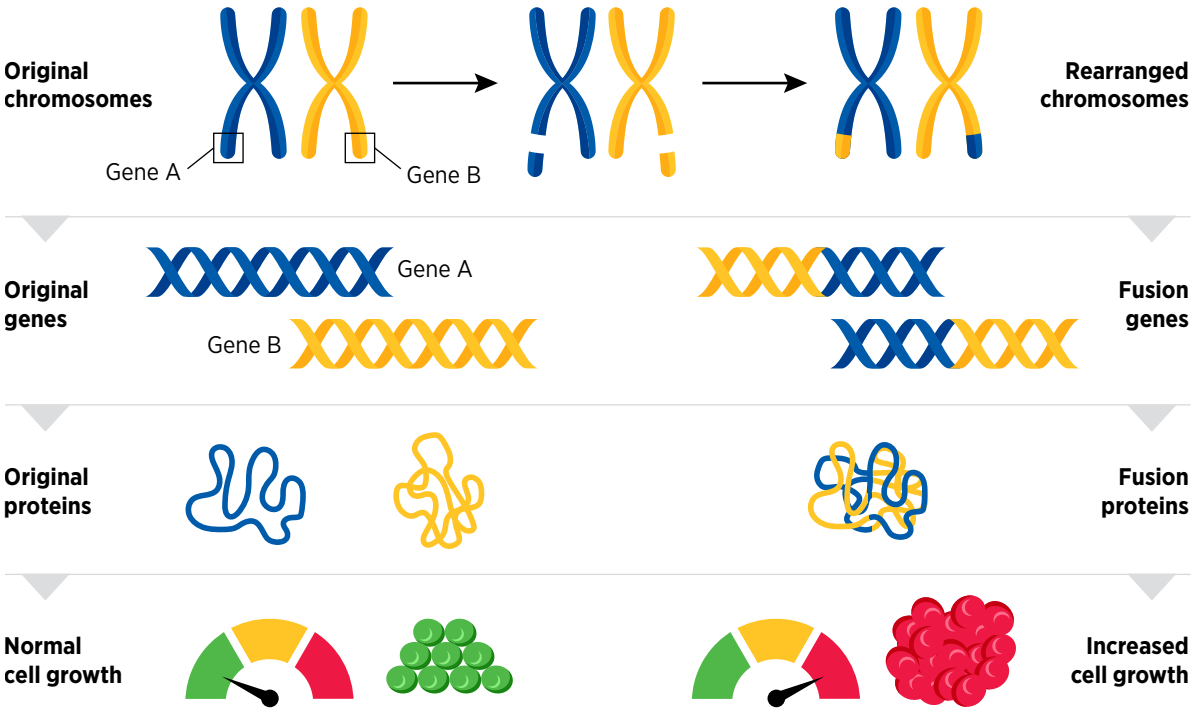
	Blood Cancers	Solid Tumors
ORIGIN	Arise in bone marrow or lymphoid tissues, such as thymus and spleen.	Begin as localized masses in organs.
GENETIC ALTERATIONS	Lower number of genetic alterations, largely driven by structural changes in genes.	Higher number of genetic alterations, largely driven by single nucleotide changes.
EPIGENETIC CHANGES	Genomes marked by lower than average levels of DNA methylation; frequently carry mutated forms of epigenome-modifying proteins.	Genomes marked by higher than average levels of DNA methylation; sporadically carry mutated forms of epigenome-modifying proteins.
PRECANCEROUS STATES	Well-characterized precancerous states that are identifiable from blood sample years before cancer.	Less well-characterized precancerous lesions that are not easily identifiable and often require invasive biopsy.
CANCER GROWTH	Less dependent on low oxygen conditions.	Low oxygen conditions are required for blood vessel formation in and around the tumor.
METASTASIS	"Metastasis" is effectively the first step—cancerous cells can enter bloodstream very early.	Cancer cells must undergo complex changes to leave the tissue of origin, enter bloodstream, and grow in other organs.
TREATMENT OPTIONS	Mostly chemotherapy, molecularly targeted therapy, and immunotherapy; surgery and radiation are rarely used.	Early-stage cancers traditionally treated with surgery or radiation; chemotherapy, molecularly targeted therapy, and immunotherapy are added for advanced stages.
DISEASE MONITORING	Cancer cells/DNA naturally present in peripheral blood, enabling routine testing of minimal residual disease.	Combination of imaging and biomarkers often used; circulating tumor DNA shed irregularly depending on tumor size and location; currently investigational.

chromosomal rearrangements; about 30 percent of leukemias, lymphomas, and multiple myeloma carry chromosomal rearrangements, compared to roughly 5 percent to10 percent of solid tumors (696). In fact, the first chromosomal rearrangement between chromosomes 9 and 22 and the resulting *BCR-ABL1* fusion gene was described in CML (see **Figure 21**, p. 148). The higher frequency of chromosomal translocations in blood cancers partly reflects the biology of hematopoietic cells, which are naturally programmed to rearrange their DNA to produce diverse antibodies and other proteins against pathogens.

Many subtypes of blood cancers are very rare—those with fewer than 15 cases out of 100,000 people each year. Among some of the blood cancer subtypes with less than 1 case out of 100,000 people every year are rare leukemias (e.g., hairy cell leukemia, acute promyelocytic leukemia), rare lymphomas (e.g., mantle cell lymphoma, anaplastic large cell lymphoma),

FIGURE 22

Generation of Fusion Proteins Through Chromosomal Rearrangements



Chromosomal rearrangements, also called chromosomal translocations, occur due to errors in cell division, whereby genes present on different chromosomes (depicted as Gene A and Gene B) fuse together to give rise to fusion genes that are not present in normal cells (shown as multicolor genes). Proteins made from fusion genes often have the properties to hijack and deregulate normal cellular mechanisms, such as cell growth, to drive cancer development.

and other rare hematologic malignancies (e.g., Waldenström macroglobulinemia). As is the case with other rare cancers, rare blood cancers suffer from lack of expertise across the research and care continuum (see **Sidebar 38**, p. 122), underscoring the urgent need for sustained investment in foundational and translational research.

Precision Medicine Driving Advances Against Blood Cancers

Decades of research leading to major advances in blood cancer treatments have laid the groundwork for a new era of oncology that transcends traditional boundaries between hematologic and solid tumors. Blood cancers, particularly myeloma, have also served as models for developing therapeutic strategies that not only target the cancer cells directly but also invoke the immune system to destroy cancer cells (697).

Pioneering successes in the development of molecularly targeted therapies for blood cancers introduced the concept that cancer can be effectively treated by selectively targeting its genomic drivers rather than focusing on its site of origin. As one example, imatinib—the first molecularly targeted therapy—transformed once-fatal CML)into a manageable condition by blocking the BCR-ABL1 protein that drives the disease (698,699). On the basis of recent findings, some CML patients with deep, sustained responses can stop taking imatinib entirely and remain in remission while enjoying a better quality of life (700).

A decade after the approval for CML, FDA expanded the use of imatinib for a rare digestive tract cancer known as gastrointestinal stromal tumor (GIST). This approval was based on research showing that many GISTs are driven by activating

TABLE 9

A Selected List of Repurposed FDA-approved Precision Medicine Drugs

Blood Cancer Therapeutics With Expanded Use in Solid Tumors and Rarer Cancers

DRUG		SHARED FEATURE	FIRST APPROVAL		EXPANDED APPROVAL	
Generic Name	Trade Name		In	For	In	For
imatinib	Gleevec	BCR-ABL1 protein	2001	CML	2008	Gastric cancer
ivosidenib	Tibvoso	*IDH1* mutation	2018	AML	2021	Bile duct cancer
zanubrutinib	Brukinsa	Activated BTK protein	2019	MCL	2021	Waldenström's macroglobulinemia

Solid Tumor Therapeutics With Expanded Uses in Blood and Rare Cancers

DRUG		SHARED FEATURE	FIRST APPROVAL		EXPANDED APPROVAL	
Generic Name	Trade Name		In	For	In	For
crizotinib	Xalkori	*ALK* mutation	2011	Lung cancer	2021	ALCL
vemurafenib	Zelboraf	*BRAF* mutation	2011	Melanoma	2017	Erdheim-Chester disease
avapritinib	Ayvakit	*PDGFR* mutation	2020	Gastric cancer	2021	Mastocytosis
pemigatinib	Pemazyre	*FGFR1* mutation	2020	Bile duct cancer	2022	Myeloid/lymphoid neoplasms
tazemetostat	Tazverik	*EZH2* mutation	2020	Soft tissue sarcoma	2020	FL

Blood Cancer Therapeutics With Expanded Uses Beyond Cancer

DRUG		SHARED FEATURE	FIRST APPROVAL		EXPANDED APPROVAL	
Generic Name	Trade Name		In	For	In	For
ofatumumab	Arzerra	CD20 protein	2010	CLL	2020	Multiple sclerosis
ruxolitinib	Jakafi	Activated JAK protein	2011	Myelofibrosis	2019	cGVHD
ruxolitinib	Jakafi	Activated JAK protein	2012	Myelofibrosis	2021	Atopic dermatitis
ibrutinib	Imbruvica	Activated BTK protein	2013	MCL	2017	Steroid-refractory chronic GVHD
daratumumab	Darzalex	CD38 protein	2015	MM	2021	Systemic light chain amyloidosis

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; BCR-ABL1, breakpoint cluster region–Abelson murine leukemia viral oncogene homolog 1; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CD20, cluster of differentiation 20; CD38, cluster of differentiation 38; CML, chronic myeloid leukemia; cGVHD, chronic graft-versus-host disease; EZH2, enhancer of zeste homolog 2; FGFR1, fibroblast growth factor receptor 1; FL, follicular lymphoma; GVHD, graft-versus-host disease; IDH1, isocitrate dehydrogenase 1; JAK, Janus kinase; MCL, mantle cell lymphoma; MM, multiple myeloma; PDGFR, platelet-derived growth factor receptor.

mutations in the KIT protein, another target of imatinib in addition to BCR-ABL1 (692,701–703). Long-term follow-up confirmed that GIST patients who stayed on imatinib had far better disease control and survival than those who stopped, with benefits growing over time (704). By underscoring that a therapeutic to treat blood cancers could change the outlook for patients with a solid tumor, imatinib has ushered in a new paradigm of precision cancer medicine (see **Figure 21**, p. 148).

The development and success of imatinib inspired a new generation of small molecule inhibitors targeting genomic drivers in blood cancers, and now similar strategies are being used to target common alterations in solid tumors, such as those in *BRAF*, *NTRK*, *IDH1/2*, *RET*, and *FGFR* genes (705). More specifically, it established the family of protein kinases as viable therapeutic targets, paving the way for the approval of more than 80 kinase inhibitors by FDA (706). While most current FDA approvals for these molecularly targeted therapeutics remain limited to solid tumors, many of these same genomic alterations also exist—and are targetable—in blood cancers.

Several therapeutics that were initially FDA-approved to treat blood cancers have been subsequently approved to treat solid tumors, and vice versa (see **Table 9**, p. 155). An integrated

approach that applies lessons learned from one field to the other promises not only more efficient drug development but also broader therapeutic access and innovation for more patients across the cancer spectrum (707).

Repurposing existing drugs for new uses beyond their approved indications is particularly important to speed progress against rarer blood cancers that share treatable molecular targets with solid tumors or more common blood cancers (708,709). As an example, a basket trial, the clinical study that groups patients by genetic features (see **Sidebar 28**, p. 91), enabled the 2017 FDA approval of vemurafenib (Zelboraf), first approved in 2011 for melanoma, to treat Erdheim-Chester disease, an ultra-rare hematologic malignancy. Between 50 percent and 70 percent of patients with Erdheim-Chester disease harbor *BRAF* gene mutations, the same alteration that is common in melanoma and targeted by the BRAF inhibitor vemurafenib. Studies have shown that patients with Erdheim-Chester disease responded well to vemurafenib treatment (710–712).

Although long-term follow-up studies have also shown serious side effects (713), the generally favorable response to vemurafenib in patients with Erdheim-Chester disease illustrates how knowledge from one cancer type can inform another (712). This example also underscores the importance of integrating genomics, molecular diagnostics, and cross-disciplinary collaboration to identify actionable mutations and develop treatments for understudied malignancies.

In the following sections, we present a broad overview of some of the transformative advances in precision medicine from the past decade that are being used in the clinic for patients with different types of blood cancers.

Diagnosing Blood Cancers With Increasing Precision

Over the past decade, breakthroughs in sequencing technologies, biospecimen processing, and computational biology have fueled innovations in molecular diagnostics for hematologic malignancies (714). In addition to foundational technologies, such as imaging for detection of chromosomal alterations and polymerase chain reaction—which enables amplifying DNA amount from a sample—for detection of minimal residual disease, next-generation sequencing of cancer DNA and RNA has now become a standard for diagnosis, prognosis, and therapeutic decision-making (see **Modernizing Clinical Trial Design for Blood Cancers**, p. 174) (715). AML—the deadliest form of blood cancer (see **Table 7**, p. 147), with relapse rates still around 40 percent to 50 percent—is just one example for which rapid and tailored molecular profiling is becoming more crucial (716).

Innovations like loop-mediated isothermal amplification sequencing, which combines rapid increase in the amount of DNA and RNA as well as their sequencing from very small amounts of blood, are helping to identify the genetic alterations in hematologic malignancies within 2 days, sometimes within hours (717,718). Because chromosomal alterations play a pivotal role in many blood cancers, detecting these structural variations with speed and accuracy is key to informing clinical decisions. In this regard, optical genome mapping, a high-resolution imaging technique that allows long stretches of DNA to be examined under the microscope for detecting even the most complex structural variations in chromosomes, is proving vital in gathering clinically relevant information about a patient's cancer (719). Similarly, tests that identify methylation patterns in genomes of patients with AML are unraveling epigenetic underpinnings of the disease and are at the cusp of broader clinical use for diagnosing AML (see **Epigenetic Changes**, p. 40) (720,721).

The emergence of single-cell sequencing has dramatically reshaped the understanding of blood cancers, revealing great heterogeneity in their transcriptomes, epigenomes, and cellular characteristics, even within the same subtype (722). These technologies have identified unique features not only of cancer cells overall but also of those cancer cell populations that confer resistance to treatment (723), knowledge that can help design more effective therapies. Parallel strides in computational biology are reshaping how data derived from these technologies are interpreted.

However, many of these state-of-the-art approaches require significant investments in specialized expertise and infrastructure, making them out of reach for many researchers and patients alike (714). While remarkable progress has been made for diagnosing blood cancers, additional work is needed to overcome major hurdles in translating these technological gains into universal, precise, and accessible care for patients with blood cancers.

A Revolution in Molecularly Targeted Therapies

Over the past decade, molecularly targeted therapies have transformed the treatment landscape for blood cancers. Advances in genomic profiling have identified the genetic alterations in blood cancers, which has enabled the development of drugs that precisely inhibit mutated forms of proteins, such as BTK, BCL-2, FLT3, and IDH, that drive uncontrollable proliferation and growth of cancer cells. These therapies offer deeper responses, prolonged survival, and improved quality of life. This section provides a broad overview of the key advances that have revolutionized treatment options for patients with blood cancers.

Breakthroughs in Treating Leukemias

Over the past two decades, the treatment of leukemia has undergone a profound transformation, moving away from a

TABLE 10

FDA-approved New Molecularly Targeted Therapies Against Leukemias (2015–2025)

Approved For	Approved In	Generic Name	Trade Name	What It Is
ALL, AML	November 2024	revumenib	Revuforj	Epigenome-modifying agent
AML	July 2023	quizartinib	Vanflyta	Cell-signaling inhibitor
AML	December 2022	olutasidenib	Rezlidhia	Epigenome-modifying agent
CML	October 2021	asciminib	Scemblix	Cell-signaling inhibitor
AML	November 2018	gilteritinib	Xospata	Cell-signaling inhibitor
AML	November 2018	venetoclax	Venclexta	Cell-signaling inhibitor
AML	November 2018	glasdegib	Daurismo	Cell-signaling inhibitor
AML	July 2018	ivosidenib	Tibsovo	Epigenome-modifying agent
AML	September 2017	gemtuzumab ozogamicin	Mylotarg	Cell-lysis mediator
ALL	August 2017	inotuzumab ozogamicin	Besponsa	Cell-lysis mediator
AML	August 2017	enasidenib	Idhifa	Epigenome-modifying agent
AML	April 2017	midostaurin	Rydapt	Cell-signaling inhibitor
CLL	April 2016	venetoclax	Venclexta	Cell-signaling inhibitor

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia.

reliance on chemotherapy toward therapies designed to target the specific molecular drivers of disease (see **Table 10**, p. 157). Uncovering the molecular underpinnings of CML pioneered this revolution, whereby the discovery of the Philadelphia chromosome and the resulting *BCR-ABL1* fusion gene led to the development of small molecule inhibitors, such as imatinib, specifically targeting functions of the abnormal BCR-ABL1 protein (see **Figure 21**, p. 148). Imatinib, which was approved by FDA for CML treatment in 2001, remains the gold standard today (698).

Newer and improved BCR-ABL1 inhibitors, such as dasatinib, nilotinib, bosutinib, and ponatinib, have since emerged, offering options in the face of resistance mutations like T315I that render imatinib ineffective (724). Most recently, in 2021, FDA approved asciminib, a first of its kind BCR–ABL1-targeted treatment that binds to a different active site of the protein than any of the drugs indicated above and persistently blocks the activity of the mutated form of BCR-ABL1. Thanks to these treatments, CML has been transformed from a disease with a typical life expectancy of 3 to 5 years into one in which most patients can expect to live a normal lifespan.

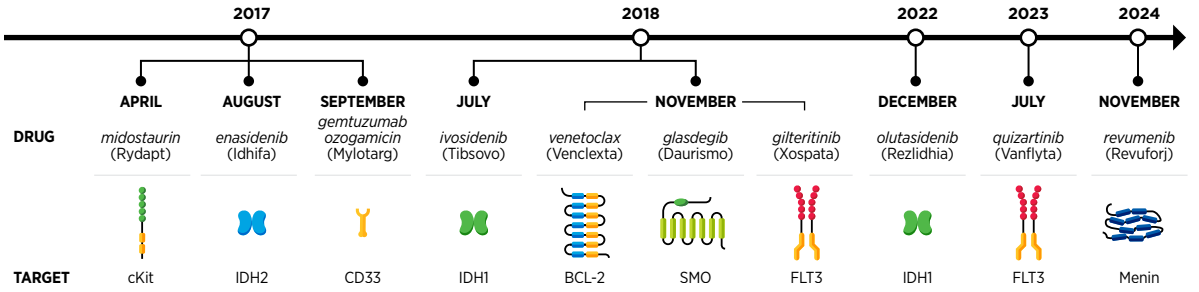
The approach of targeting key proteins involved in cancer cell proliferation, growth, and survival has since been extended to AML (see **Figure 23**, p. 158). As one example, mutations in the *FLT3* gene—which is involved in proliferation and survival of hematopoietic stem and progenitor cells—are present in roughly one-third of patients with AML. In 2017, FDA approved the first molecularly targeted therapeutic, midostaurin (Rydapt), to treat AML patients whose cancer cells harbor *FLT3* mutations (725). Since then, two additional molecularly targeted therapeutics—gilteritinib (Xospata) and quizartinib (Vanflyta)—have been approved by FDA to treat patients with AML. Each of the three therapeutics has helped patients with AML live longer and without detectable disease (726–730).

Another major advance in the personalized treatment of AML has been the development of therapeutics targeting IDH1 and IDH2—important proteins that mediate a key step in cellular energy production and epigenome regulation (731). Mutated forms of IDH1/2, found in approximately 20 percent of AML cases, promote the development of leukemia (732). As of June 30, 2025, FDA has approved three IDH inhibitors for AML—ivosidenib (Tibsovo) in 2017, enasidenib (Idhifa) in 2018, and olutasidenib (Rezlidhia) in 2022—all of which have shown a complete remission in 20 percent to 40 percent of patients with AML (733). Targeting IDH1/2 mutations in solid tumors have also shown great promise (see **Bringing the Promise of Precision Medicine to Children, Adolescents, and Young Adults With Cancer**, p. 123) (734), further underscoring how knowledge gleaned from the underpinnings of hematologic malignancies is driving progress against certain solid tumors.

During the 12 months covered by this report (July 1, 2024 to June 30, 2025), FDA further expanded its armamentarium of AML therapies by approving revumenib (Revuforj), a new

FIGURE 23

Molecularly Targeting Vulnerabilities of Cancer Cells in Acute Myeloid Leukemia



Acute myeloid leukemia (AML) is a particularly intractable blood cancer, with high mortality and low survival rates. For decades, the standard of care for patients with AML was chemotherapy. This changed in 2017 when the US Food and Drug Administration (FDA) approved the first molecularly targeted therapeutic, midostaurin (Rydapt), for treating AML patients who carried mutations in the *cKit/FLT3* gene, which is involved in cell survival and proliferation. Since then, FDA has approved two new and improved therapeutics—gilteritinib (Xospata) in 2018 and quizartinib (Vanflyta) in 2023—to treat patients with AML who carry mutations in the *FLT3* gene.

Thanks to decades of research, within the past decade, precision medicine options for patients with AML have expanded considerably. In addition to the three therapeutics for treating patients with AML who carry the *FLT3* alterations, FDA has approved several molecularly targeted therapeutics inhibiting the activity of proteins involved in modifying the epigenome (enasidenib [Idhifa] in 2017, ivosidenib [Tibsovo] in 2018, olutasidenib [Rezlidhia] in 2022) and promoting leukemia cell survival (venetoclax [Venclexta] and glasdegib [Daurismo], both in 2018). In 2017, FDA also approved an antibody–drug conjugate, called gemtuzumab ozogamicin (Mylotarg), to treat patients whose leukemia cells carry CD33 protein; this therapeutic works by bringing a toxic compound directly to leukemia cells.

In November 2024, FDA approved another key molecularly targeted therapeutic revumenib (Revuforj). Revumenib works by blocking the interaction between menin and MLL1. By binding to menin, it prevents the menin–MLL1 complex from attaching to DNA, thereby halting the abnormal genetic programs that fuel leukemia. As a result, leukemia cells are either driven to mature into healthy blood cells or are eliminated. The therapeutic is approved for adult and pediatric patients (1 year and older) with acute leukemia harboring *KMT2A* rearrangements who never responded to or experienced relapse after initial treatments.

molecularly targeted treatment for patients, including children, who carry a common structural variation in the *KMT2A* gene. Structural variations, also known as rearrangements, in the *KMT2A* gene are observed in 80 percent of infants with 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 (see **Sidebar 43**, p. 146) (735).

The *KMT2A* gene encodes a protein called MLL1, which plays a critical role in normal blood cell development by regulating gene expression through epigenetic mechanisms. When the *KMT2A* gene is rearranged, it disrupts normal cell development by causing blood cells to revert to an immature, stem cell–like state, preventing them from maturing into functional blood cells. This process is driven by the interaction of MLL1 with another protein called menin. Together, menin and MLL1 form a complex that binds to DNA in the cell nucleus and triggers harmful genetic programs that lead to leukemia. Acute leukemia with *KMT2A* rearrangements is associated with treatment resistance and poor prognosis (736). In addition to *KMT2A*

MORE THAN 25%

Childhood leukemia represents more than 25% of all **new childhood cancer cases**.

Source: (4).

W61

rearrangements, mutations in the *NPM1* gene—detected in up to 30 percent of acute AML cases in adults—also depend on menin to promote leukemia development (737).

These discoveries led to the development of menin-targeted therapies (738), culminating in the November 2024 FDA approval of revumenib (Revuforj), the first menin inhibitor, for adult and pediatric patients (1 year and older) with acute leukemia harboring *KMT2A* rearrangements who never responded to or experienced relapse after initial treatments. Revumenib works by blocking the interaction between menin and MLL1. By binding to menin, it prevents the menin–MLL1 complex from attaching to DNA, thereby halting the abnormal genetic programs that fuel leukemia. As a result, leukemia cells are either driven to mature into blood cells with some normal properties or are eliminated.

FDA approval was based on a phase I/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). The benefits lasted a median of over 6 months. Revumenib has provided patients such as **John C. (Jack) Moorman** (see p. 160) with a personalized treatment option that is much less aggressive than traditional chemotherapeutics.

Ongoing studies are looking to identify mechanisms of resistance to revumenib treatment and evaluating revumenib as the initial treatment as well as in combination with other molecularly targeted therapeutics or chemotherapeutics to improve outcomes for patients.

Molecularly targeted therapies have significantly advanced the treatment of ALL, especially in certain subtypes and relapsed/refractory disease. Approximately 20 percent to 30 percent of adult ALL cases are Philadelphia chromosome–positive (Ph+ ALL), while among children, the prevalence is much lower at about 2 percent to 5 percent (739). Ph+ ALL is driven by the Philadelphia chromosome product, the BCR-ABL1 fusion protein, molecularly targeted therapeutics against which have revolutionized treatment of Ph+ ALL, in addition to CML.

Another class of molecularly targeted therapeutics that is gaining momentum in the treatment of blood cancers comprises antibody–drug conjugates (ADCs) (see **Delivering Cytotoxic Agents Precisely to Cancer Cells**, p. 113). Unlike the therapeutics discussed thus far in this section—all are small molecules inhibiting functions of one or more proteins in the cells—ADCs kill cancer cells in an entirely different manner (740).

Inotuzumab ozogamicin (Besponsa), an ADC, was approved by FDA in 2017, for treating patients with Ph+ ALL. ADCs represent an exciting new class of molecularly targeted therapeutics that function by finding certain proteins present on the surface of cancer cells and then delivering toxic compounds directly to them, thus minimizing side effects from the treatment (740). Combining these molecularly targeted therapies with chemotherapeutics or immunotherapeutics has transformed outcomes for patients with ALL, with about 73 percent of patients living 5 years or more following diagnosis (4,739).

Despite the expanding number of precision medicine drugs against leukemia, resistance to molecularly targeted therapy remains a universal challenge. Thanks to research, combining different classes of precision therapeutics with traditional forms of treatment, often tailored to a patient's molecular profile, is helping to increase remissions, delay relapses, and in some cases, eliminate the need for chemotherapy altogether. For example, treating patients who have CLL with a combination of two molecularly targeted therapies (venetoclax [Venclexta], which triggers leukemia cell death, and acalabrutinib [Calquence], which blocks leukemia cell proliferation), along with an immunotherapeutic (obinutuzumab [Gazyva], which invokes the immune system to kill leukemia cells) kept the disease from progressing in more people at 3 years than was found with standard chemotherapy (741). The treatment was also generally safe and well tolerated.

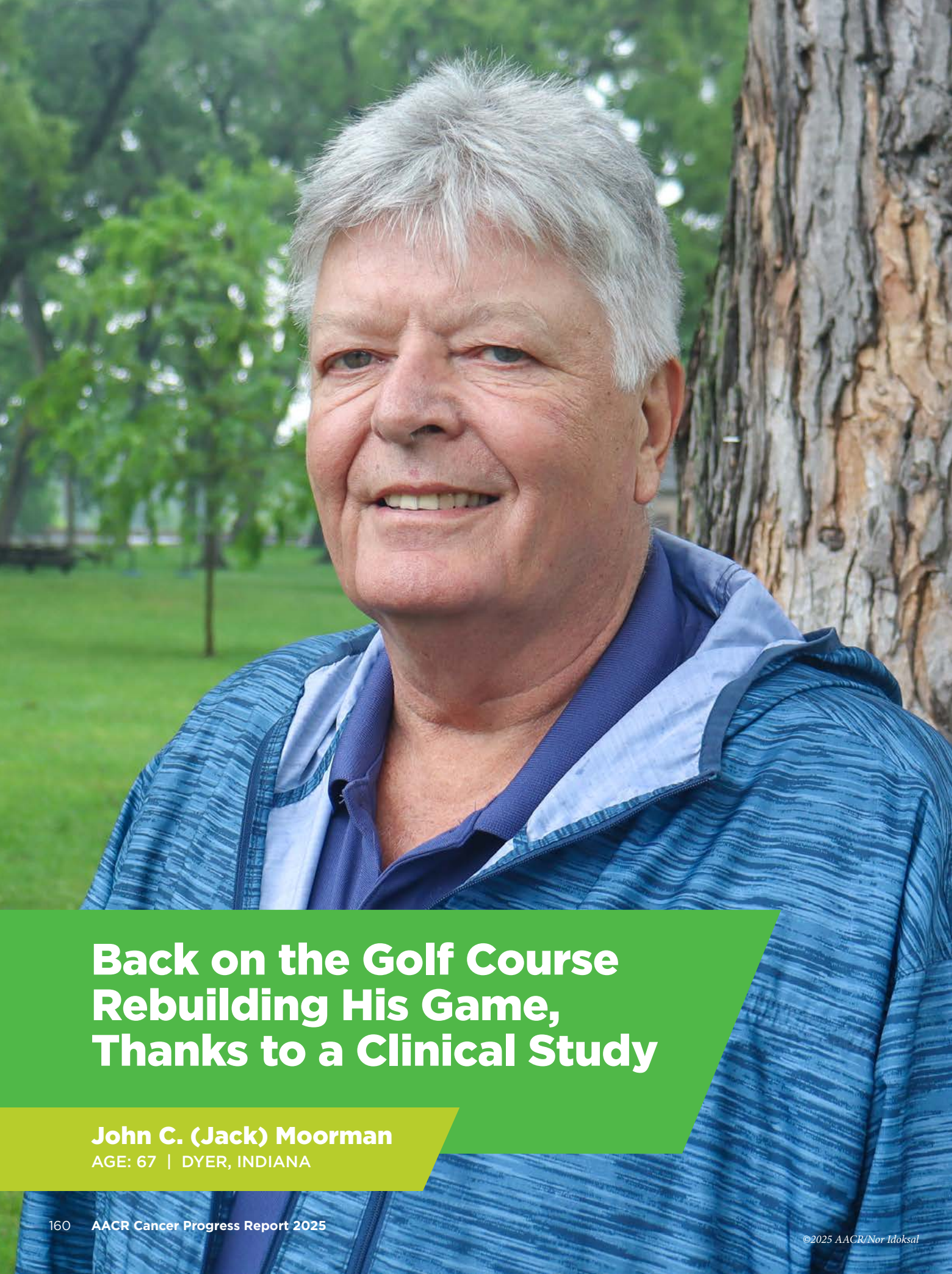
Milestones in Managing Lymphomas

In recent years, the therapeutic landscape for NHL has undergone a profound shift, offering new hope for patients who historically had limited options beyond chemotherapy. This shift reflects a deeper understanding of lymphoma biology and the identification of proteins that can be selectively inhibited with targeted therapies (see **Table 11**, p. 162). As a result, molecularly targeted therapies are reshaping treatment across major NHL subtypes by improving survival, enhancing quality of life, and reducing treatment-related toxicity (742).

NHL is the most common type of blood cancer, with over 80 subtypes (see **Lymphomas**, p. 149). Some common forms include DLBCL, which is the most aggressive and diagnosed subtype (about 30 percent to 35 percent of NHL cases); follicular lymphoma (FL), 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 (662). Over the past decade, an expanding number of molecularly targeted therapies have become available for patients with DLBCL, FL, and MCL, leading to notable gains in response rates and durability of remission (743–745).

One protein that has become an attractive target for developing targeted therapies against NHL is Bruton's tyrosine kinase

continued on page 162



Back on the Golf Course Rebuilding His Game, Thanks to a Clinical Study

John C. (Jack) Moorman
AGE: 67 | DYER, INDIANA

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In May 2023, Jack Moorman was feeling great. He walked 5 miles each day with his wife through Wicker Memorial Park in Highland, Indiana. At 65, retired and in good shape, he was focused on staying active and enjoying life between his home in Indiana and snow birding in Florida. The only reason he went to his doctor was a billing issue with Medicare. It may have saved his life.

Routine bloodwork revealed that his white blood cell and platelet counts were abnormally low. Initially suspecting an infection, his primary care doctor recommended a follow-up. Weeks later, a rheumatologist ordered a bone marrow biopsy. The diagnosis came on June 1, 2023: acute myeloid leukemia (AML)—specifically, an intermediate-risk subtype with a high risk of relapse. "I was asymptomatic. If I had not gone in, they told me I would be dead," said Jack.

Jack's local oncologist referred him to the University of Chicago, where he met Dr. Anand Patel, an encounter Jack now calls the most important 75-minute conversation of his life. Together, they discussed treatment options, including intensive chemotherapy typically reserved for younger patients.

But Dr. Patel offered something else: a spot in a clinical trial testing a new targeted therapy called revumenib, as part of the Beat AML trial. Jack had a specific genetic mutation—KMT2A translocation—for which revumenib was designed. With only one spot left in the trial, he did not hesitate. "I got the last seat," remembers Jack.

The timing was critical. Between his June 1 diagnosis and a June 8 enrollment in the trial, the leukemia cells in Jack's bone marrow increased from 30 percent to 82 percent. The treatment combined the investigational targeted therapy, revumenib, with two other established AML treatments, azacitidine and venetoclax. After just one 28-day cycle, Jack achieved complete remission.

Due to the high relapse risk associated with his mutation, his care team recommended a stem cell transplant. It would mean replacing his immune system entirely, which involves months of grueling recovery but can result in a cure. His sisters were not a match. Instead, a donor was located overseas. Because of scheduling delays, Jack had to wait several months.

In the meantime, he underwent two more treatment cycles to keep the cancer at bay. The second course, unlike the first, hit hard. He was hospitalized for 3 weeks with severe side effects, including cardiac complications, gout, and blood in his urine. His resolve never wavered. "The second cycle knocked me down. But I knew I had to get to the transplant," Jack said.

On October 23, 2023, Jack received his stem cell transplant. Jack credits his stem cell oncologist, Dr. Miriam Nawas, whose expertise and compassionate care guided him through a successful transplant. It came in the form of eight bags of donated cells, what he jokingly called "applesauce." His immune system was wiped out, requiring platelet transfusions and constant monitoring. Though he experienced graft-versus-host disease, it appeared only as a treatable rash. A bigger challenge came later—nutritional malabsorption, which caused him to lose 50 pounds and significant muscle mass. But even then, he tried to keep up with his walking as much as he could.

Throughout treatment, Jack maintained fierce intellectual curiosity. He asked detailed questions, challenged assumptions, and became a model of engaged patienthood. "They had to keep up with me," he said of his care team, "and they did. They earned my trust. I am a control freak. But I knew I had to trust the experts—and they saved my life."

By early 2024, Jack was in excellent shape. His leukemia remained in remission. He had regained nearly all his lost strength and was back to walking daily. He now receives maintenance chemotherapy, a reduced dose of venetoclax taken orally for 14 days each month.

Jack's story is personal, but also generational. His father, too, was saved by cancer research. Diagnosed decades earlier with chronic myeloid leukemia (CML), his father received imatinib, one of the earliest targeted therapies ever developed. It turned a once-fatal disease into a manageable condition. His dad lived for 15 additional years. "Cancer research saved my father's life. Now it has saved mine," said Jack.

The parallels between father and son underscore Jack's call to action. "This is a complex disease," he said. "But every day, researchers are chipping away at it. And we are living proof that their work matters."

To Congress and the public, Jack is blunt. "If we cut cancer research funding, people will die needlessly," he said. "These breakthroughs do not happen by accident; they take time, science, and support. I want everyone to have the chance I got."

Today, Jack's life has largely returned to normal, though he is still rebuilding his golf game. "I lost two clubs of distance," he joked—but otherwise he feels like himself. He continues his monthly blood tests "I feel terrific. Like I did before I had cancer. Maybe even better—because now, I know how lucky I am."

"Cancer research saved my father's life. Now it has saved mine."

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

TABLE 11

FDA-approved New Molecularly Targeted Therapies Against Lymphomas (2015–2025)

Approved For	Approved In	Generic Name	Trade Name	What It Is
CTCL	August 2024	denileukin diftitox-cxdl	Lymphir	Cell-signaling inhibitor
CLL/SLL	January 2023	pirtobrutinib	Jaypirca	Cell-signaling inhibitor
LBCL	April 2021	loncastuximab tesirine-lpyl	Zynlonta	DNA-damaging agent
FL	January 2020	tazemetostat	Tazverik	DNA-repair Inhibitor
MCL	November 2019	zanubrutinib	Brukinsa	Cell-signaling Inhibitor
DLBCL	June 2019	polatuzumab vedotin-piiq	Polivy	Cell-lysis mediator
CLL/SLL	October 2017	acalabrutinib	Calquence	Cell-signaling inhibitor
CLL/SLL	April 2016	venetoclax	Venclexta	Cell-lysis mediator

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma.

(BTK). Research has shown that BTK plays a crucial role in B-cell development, survival, and proliferation. In certain lymphomas, BTK becomes overactive, making it a central contributor to the disease and an ideal target for therapy (746). Small molecules inhibiting BTK function have been especially transformative in treating various subtypes of NHL.

As of June 30, 2025, FDA has approved four BTK inhibitors: ibrutinib, approved in 2013; acalabrutinib, approved in 2017; pirtobrutinib (Jaypirca), approved in 2023; and zanubrutinib (Brukinsa), approved in 2024. These molecularly targeted therapies have been approved to treat several NHL subtypes, as well as certain types of hematologic malignancies that can progress into lymphomas (see **Table 11**, p. 162) (747). Although ibrutinib is the first FDA-approved BTK inhibitor, the newer three inhibitors have improved selectivity, reduced off-target effects, and address treatment resistance. Pirtobrutinib, for instance, has a unique mechanism of action that makes it effective even against mutated forms of BTK that are resistant to other BTK-targeted therapeutics. Collectively, these therapeutics have enabled durable responses with less toxicity in many patients with NHL (747).

Researchers have also leveraged another cellular process, called apoptosis or programmed cell death, to develop molecularly targeted therapeutics that induce cell death in lymphomas (748). In normal cells, apoptosis is a tightly controlled process, in which members of the BCL family of proteins play important roles in preventing cell death in healthy cells and triggering apoptosis in damaged or unhealthy cells. Cancer cells, including some lymphoma subtypes, often have higher levels of proteins that prevent cell death, thus helping them escape apoptosis (748).

In 2016, FDA approved venetoclax for the treatment of CLL in which part of a chromosome is deleted, and extended this approval in 2018 for CLL or SLL with the same genetic alteration. Venetoclax selectively inhibits the activity of BCL-2, a member of the BCL protein family, that prevents lymphoma cells from dying. In 2020, FDA approved selinexor (Xpovio), which also triggers lymphoma cell death, albeit by a different mechanism. Selinexor was approved for the treatment of DLBCL, the most common and most aggressive form of NHL.

ADCs are also proving effective in the treatment of NHL. As of June 30, 2025, FDA has approved three ADCs to treat different NHL subtypes (see **Table 11**, p. 162). Polatuzumab vedotin (Polivy), approved in 2019, targets a protein called CD79b, which is abundantly present on the surface of lymphoma cells. Since its approval, polatuzumab vedotin has emerged as a major addition to the treatment of relapsed/refractory DLBCL, particularly in combination with bendamustine, a chemotherapeutic, and rituximab, another molecularly targeted therapeutic (749). Because of its selective mechanism—delivering cytotoxic agents directly into lymphoma cells—the therapeutic also has reduced toxicity.

The other two ADCs approved for treatment of lymphoma subtypes, loncastuximab tesirine-lpyl for large B-cell lymphoma and brentuximab vedotin for ALCL, bind to two different proteins, CD19 and CD30, on the lymphoma cell surface (750). In MCL, a highly aggressive type of NHL, ADCs are increasingly being studied in combination with other molecularly targeted therapeutics to overcome resistance to chemotherapy (751).

While much of the therapeutic progress has focused on the more common B-cell subtypes of NHL, researchers are also advancing novel treatments for rarer and clinically distinct forms of the disease, such as cutaneous T-cell lymphoma (CTCL), which mainly affects the skin. Early-stage CTCL tends

TABLE 12

FDA-approved New Molecularly Targeted Therapies Against Multiple Myeloma (2015–2025)

Approved In	Generic Name	Trade Name	What It Is
July 2019	selinexor	Xpovio	Cell-lysis mediator
November 2015	ixazomib	Ninlaro	Proteosome inhibitor

to grow slowly and may not impact life expectancy, but about 30 percent of patients progress to advanced stages within 10 years with significant reduction in survival rates. Treatments for early-stage disease focus on managing skin symptoms and slowing disease progression, starting with topical agents or radiation, while those with advanced disease are treated with additional therapies including systemic treatments. However, current treatments for advanced CTCL often stop working within months and can cause serious side effects.

Researchers are taking innovative approaches to target CTCL. One such approach involves designing synthetic proteins that can target cancer cells and directly deliver toxic molecules to kill them. In August 2024, FDA approved denileukin diftitox-cxdl (Lymphir) for treating adults with CTCL who have received at least one prior systemic therapy and whose disease has returned or stopped responding to treatments. FDA approval was based on results from a phase III clinical trial in which 36 percent of patients responded to denileukin diftitox-cxdl and nearly 9 percent had a complete disappearance of their cancer (753).

Denileukin diftitox-cxdl consists of part of the diphtheria toxin linked to interleukin-2 (IL-2), a molecule produced by the immune system that activates immune cells to fight infections and attack cancer cells. Denileukin diftitox-cxdl targets IL-2 receptors found on both cancer cells and certain immune cells, delivering the diphtheria toxin directly to these cells. Once the drug attaches to the IL-2 receptor, it is taken into the cell, where it is broken apart to release the toxin. The toxin blocks the cell's ability to make proteins, ultimately causing cancer cells to die. In addition to attacking cancer cells, denileukin diftitox-cxdl also eliminates specific immune cells that help protect the cancer, potentially making the treatment more effective.

As research continues to illuminate the molecular underpinnings of lymphoma, the pace of therapeutic innovation has never been stronger. From small molecule inhibitors that block lymphoma survival to ADCs that directly deliver toxins to cancer cells, current treatments reflect decades of progress in basic and translational science. Sustained investment in research will be critical to maintaining this momentum—transforming even the most aggressive or treatment-resistant subtypes into manageable and, in some cases, curable diseases.

Cutaneous T-cell lymphoma patients **living in rural areas and those treated at non-academic/research facilities** had a 74% and 21% **higher risk of death**, respectively.

Source: (752).

W62

Progress in Targeting Multiple Myeloma

In recent years, the development of molecularly targeted therapies and immunotherapies has reshaped the treatment landscape of multiple myeloma (see **Table 12**, p. 163), offering new hope for patients whose disease had historically relied on conventional chemotherapy and corticosteroids (see **Sidebar 41**, p. 135, **Redirecting T Cells to Eradicate Blood Cancers**, p. 167, and **Flagging Blood Cancer Cells for Destruction by the Immune System**, p. 169). These novel approaches are driven by an improved understanding of multiple myeloma biology, processes that control plasma cell proliferation and growth, and mechanisms of drug resistance (754). As a result, a new generation of precision medicines is emerging, aimed at selectively interfering with survival pathways, stress responses, and metabolism in multiple myeloma cells (755).

A growing list of small molecule inhibitors has expanded treatment options and improved outcomes for relapsed and refractory disease. The first FDA approval of a molecularly targeted therapy to treat multiple myeloma was of bortezomib (Velcade) in 2003; bortezomib inhibits the proteasome, the cell's machinery designed to eliminate unneeded or damaged proteins. Proteasome inhibitors have been particularly effective against multiple myeloma because multiple myeloma cells rely heavily on their ability to properly manage protein production and disposal (756,757). Studies have shown that in patients with newly diagnosed myeloma, the addition of bortezomib to

TABLE 13

FDA-approved New Molecularly Targeted Therapies to Treat Other Hematologic Malignancies (2015–2025)

Approved For	Approved In	Generic Name	Trade Name	What It Is
MDS	June 2024	imetelstat	Rytelo	Cell-signaling inhibitor
Myelofibrosis	September 2023	momelotinib	Ojjaara	Cell-signaling inhibitor
MLNs	August 2022	pemigatinib	Pemazyre	Angiogenesis inhibitor
Mastocytosis	June 2021	avapritinib	Ayvakit	Cell-signaling inhibitors
MPN	August 2019	fedratinib	Inrebic	Cell-signaling inhibitor
BPDCN	December 2018	tagraxofusp-erzs	Elzonris	Cell-lysis mediator
ECD	November 2017	vemurafenib	Zelboraf	Cell-signaling inhibitor

BPDCN, blastic plasmacytoid dendritic cell neoplasm; ECD, Erdheim-Chester disease; MLNs, myeloid/lymphoid neoplasms; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasm.

immunomodulatory agents such as lenalidomide (Revlimid) and dexamethasone resulted in significantly improved progression-free and overall survival with manageable side effects (758).

In 2012, FDA approved a second proteosome inhibitor, carfilzomib (Kyprolis), and in 2015, a third proteosome inhibitor, ixazomib (Ninlaro), to treat patients with multiple myeloma. All three therapeutics induce multiple myeloma cell death by disrupting protein degradation pathways, and have improved outcomes with less serious side effects (754). In addition, unlike bortezomib, which is administered either subcutaneously or intravenously, or carfilzomib, which is administered intravenously, ixazomib is given orally and is more convenient for some patients.

In 2019, FDA approved selinexor (Xpovio), which also triggers apoptosis but by trapping certain proteins in the multiple myeloma cell nucleus, where they can restore control over cell growth and trigger cancer cell death. Since its approval, selinexor has proven to be an effective treatment for multiple myeloma. A recent study showed that a combination of selinexor with bortezomib, lenalidomide, and dexamethasone achieved a 100 percent overall response rate (see **Sidebar 32**, p. 101) in newly diagnosed patients with a particularly aggressive form of multiple myeloma. The combination was well tolerated with manageable side effects, highlighting its potential as an effective and feasible first treatment given to this high-risk population (759).

Molecularly targeted therapeutics represent a promising frontier in management of multiple myeloma—particularly for patients ineligible for immunotherapies or those with resistant disease. As resistance mechanisms evolve, combinations of these agents, informed by the biology of multiple myeloma calls, may pave the way for durable, chemotherapy-free control of multiple myeloma.

In addition to molecularly targeted therapeutics approved by FDA to treat various subtypes of leukemia, lymphoma, and multiple myeloma, FDA has also approved a number of therapeutics to treat hematologic malignancies that can give rise to one of the three major types of blood cancers (see **Table 13**, p. 164).

Transforming Blood Cancer Treatment With Immunotherapy

Groundbreaking basic research in the field of immunology laid the foundation of modern immunotherapy, one of the most exciting new areas of cancer treatment along with molecularly targeted therapeutics (see **Advances in Treatment With Immunotherapeutics**, p. 128). Cancer immunotherapeutics leverage the natural ability of the immune system to fight cancer and have been transformative for patients with different types of blood cancer.

FDA-approved immunotherapeutics against blood cancers work in various ways including amplifying the cancer-killing ability of the immune cells, releasing the brakes on the immune system, and flagging cancer cells for destruction by the immune system.

Harnessing CAR T Cells to Treat Blood Cancers

Chimeric antigen receptor (CAR) T-cell therapy is a form of cellular immunotherapy (see **Sidebar 41**, p. 135) that has revolutionized the treatment landscape for blood cancers. As of June 30, 2025, FDA has approved seven CAR T-cell therapies, all for the treatment of blood cancers, including leukemia, lymphoma, and multiple myeloma (see **Sidebar 46**, p. 165). Collectively, CAR T-cell therapies represent a major breakthrough in the treatment of adults and children with blood cancers (760).

SIDEBAR 46

CAR T-cell Therapies Approved by the US Food and Drug Administration (FDA)

As of June 30, 2025, FDA has approved seven distinct 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**, and **mantle cell lymphoma**.
2020	Brexucabtagene autoleucel (Tecartus)	Patients with relapsed or refractory **mantle cell lymphoma**. Approved subsequently for adult patients with relapsed or refractory **B-cell precursor acute lymphoblastic leukemia**.
2017	Tisagenlecleucel (Kymriah)	Young adult patients up to age 25 with **B-cell precursor acute lymphoblastic leukemia**. Approved subsequently for adult patients with relapsed or refractory **follicular lymphoma** and **large B-cell lymphoma**.
	Axicabtagene ciloleucel (Yescarta)	Adult patients with relapsed or refractory **large B-cell lymphoma**. Approved subsequently for adult patients with relapsed or refractory **follicular lymphoma**.

Source: (764).

The first of these treatments, tisagenlecleucel (Kymriah), was approved by FDA in 2017 for the treatment of children and young adults with B-cell ALL that had not responded to standard treatments or had relapsed at least twice. Tisagenlecleucel allowed some children whose leukemia had returned or stopped responding to other treatments to experience complete remission. A long-term follow-up of patients treated with tisagenlecleucel showed that more than 60 percent were living 3 years or longer after their first infusion of CAR T cells (761). Additionally, more than 50 percent of patients were living without their disease coming back at the end of 3 years after treatment completion, suggesting that CAR T cells can lead to durable cancer control.

The second FDA-approved CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), which also became available in 2017, was shown to be the first treatment in nearly three decades to improve overall survival for patients with relapsed or refractory large B-cell lymphoma (762).

Most recently, researchers have provided the first-of-its-kind proof that the CAR T-cell therapy ciltacabtagene autoleucel

(Carvykti) can induce long-term remission and is potentially curative for patients with relapsed or refractory multiple myeloma. Based on a recent analysis, after only a single infusion of the CAR T cells, 33 percent of patients remained alive and progression-free after 5 years (763). This represents a major milestone in the treatment of multiple myeloma.

Several types of leukemia and lymphoma arise in B cells, including most cases of ALL (see **The State of Blood Cancers in 2025**, p. 144). While treatments like chemotherapy, stem cell transplants, molecularly targeted therapeutics, and immunotherapeutics including CAR T-cell therapy have improved outcomes, survival remains low for older adults and patients whose cancer comes back or does not respond to treatment. This low survival underscores the need for more effective therapies, a need that may be addressed by the most recently approved CAR T-cell therapy, obecabtagene autoleucel (Aucatzyl), approved in November 2024 for treating adults with B-cell ALL that has relapsed or become refractory to other treatments.

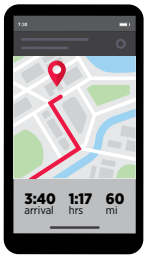
Like other CAR T-cell therapies approved for leukemia and lymphoma that arise in B cells, obecabtagene autoleucel is made by collecting a patient's T cells, multiplying them, and genetically modifying them to express a CAR that targets CD19, a protein on the surface of B cells. The modified cells are then infused back into the patient to seek out and destroy cancer cells. However, unlike existing CAR T-cell therapies, obecabtagene autoleucel is uniquely engineered with a lower binding strength to CD19, which may reduce its side effects and help the CAR T cells persist longer in the body, potentially addressing two major challenges of current CAR T treatments for B-cell ALL—high toxicity and short-lived responses (765).

FDA approval of obecabtagene autoleucel was based on results from a phase I/II clinical trial in which 42 percent of patients treated with the CAR T-cell therapy experienced a complete disappearance of their cancer within 3 months of receiving the treatment. Those who responded within 3 months stayed cancer-free for a median of about 14 months, with some patients still doing well beyond that time.

Compared to brexucabtagene autoleucel, another CAR T-cell therapy that was approved for adults with B-cell ALL in 2021, obecabtagene autoleucel caused fewer severe side effects, including lower rates of serious immune reactions and brain-related side effects (766). Notably, the severe side effects with obecabtagene autoleucel were mostly seen in patients with a high number of leukemia cells in their bone marrow, suggesting that in patients with lower disease levels the procedure may be safe as outpatient treatment.

While CAR T-cell therapies are clearly showing immense benefit for patients with blood cancer, they have many limitations including toxicities, treatment resistance, as well as barriers to manufacturing and treatment delivery.

Patients with diffuse large B-cell lymphoma living in low-income states and farther from CAR T-cell therapy centers are less likely to receive treatment. **Reducing travel distance could increase CAR T-cell therapy access by 38% nationwide.**



Source: (771).

W63

In November 2023, FDA announced that it was investigating a link between receiving CAR T-cell therapy and developing secondary cancers later on after initial clinical reports suggested a potential link. This prompted extensive investigation and a surge of research across the field (767–770). Several studies have now concluded that the risk of secondary cancer is very rare and is no greater among patients treated with CAR T-cell therapy than among those treated with other treatments.

There are disparities in the access to CAR T-cell therapies, especially among medically underserved populations (676,771). Because of serious or life-threatening immune-related adverse reactions, FDA required CAR T cells to be administered only at specially certified large academic hospitals by qualified health care professionals with appropriate medical support. However, most cancer patients receive their treatment at community settings, which limits their access to this rapidly growing class of lifesaving immunotherapies (772).

Innovations in simplifying manufacturing and broadening delivery are needed so more patients can benefit from CAR T-cell therapies. In this regard, in June 2025, FDA removed the special safety requirements for approved BCMA- and CD19-directed CAR T-cell therapies, a decision expected to expand access by allowing more treatment centers—including those in community and rural areas—to administer these therapies without additional regulatory hurdles (773).

Access to CAR T-cell therapies vary globally, with significant barriers to access in low- and middle-income countries (774). Based on an online survey of clinicians outside the United States, less than 20 percent of survey respondents reported adequate access to CAR T-cell therapies for patients with multiple myeloma (775).

To overcome some of the current limitations of CAR T-cell treatments, researchers are exploring a new generation of cell-based therapies for blood cancer (764). Innovations include CAR T cells that recognize novel targets, including those that work by binding to multiple targets on blood cancer cells, as well as their use in combination with other immunotherapies. Researchers are also exploring "universal" CAR T cells that can

be used across multiple blood cancer types (776). Additionally, to address the complex manufacturing issues, researchers are attempting to engineer CAR T cells in the patient's body instead of the laboratory, which could make them faster to produce and more affordable (777,778).

Another promising strategy involves targeting specific proteins found on AML cells to expand the use of CAR T cells to a broader patient population (779). Furthermore, the potential of natural killer (NK) cells, which can be engineered to target cancer like CAR T cells but are easier and faster to manufacture and may have fewer adverse effects, is being investigated. Together, these advances could expand access, improve safety, and enhance the effectiveness of cellular immunotherapies for a wider range of blood cancers.

Driven by its success in cancer, CAR T-cell therapies are now being evaluated in the treatment of autoimmune diseases such as lupus, in which harmful B cells drive the illness. Unlike current treatments that often leave some disease-causing B cells hidden in tissues, CAR T cells can reach difficult-to-access areas and achieve more complete B-cell elimination (780).

Unleashing the Immune System Against Blood Cancers

Immune checkpoint inhibitors (ICIs) release the brakes on immune cells, which unleashes T cells to find and destroy cancer cells. These immunotherapeutics have become the foundation of treatment for a wide range of solid tumors, including previously intractable cancers such as advanced kidney cancer, lung cancer, and melanoma, for which they have transformed patient outcomes (see **Figure 19**, p. 132). However, ICIs have had limited success in the treatment of blood cancers thus far.

Currently, the only FDA-approved ICIs for blood cancers include pembrolizumab, approved for both classic HL and a specific NHL subtype called primary mediastinal B-cell lymphoma, and nivolumab, approved for classic HL. Both are indicated for patients with relapsed or refractory disease. However, recent evidence shows that nivolumab, when combined with standard chemotherapy, can also significantly improve outcomes for patients with newly diagnosed advanced classic HL (781). This regimen was better tolerated, with fewer serious side effects, such as nerve damage, underscoring the potential of ICIs as the initial treatment for these patients.

While ICIs have shown success in treating classic HL and primary mediastinal B-cell lymphoma, they have had limited impact on other NHL subtypes, multiple myeloma, or myeloid malignancies. Researchers are exploring new immune checkpoint targets, such as LAG-3, TIM-3, TIGIT, and CD47, and developing next-generation ICIs, including bispecific antibodies that target two checkpoint proteins.

Researchers are also testing combination strategies, including pairing different ICIs or combining them with ADCs, to enhance effectiveness against blood cancers. While many of these approaches are still in early stages, ongoing and future efforts may identify patients who will benefit the most, determine the best timing for treatment, and improve long-term outcomes through optimal combinations.

Redirecting T Cells to Eradicate Blood Cancers

Certain immunotherapeutics, such as bispecific T-cell engagers (BiTEs), work by flagging cancer cells for destruction by the immune system. By attaching to cell surface proteins on T cells and cancer cells using its two arms, BiTEs bring the two cell types together, directing the T cells to home in on the cancer cells. As a result, T cells are activated, and they destroy the adjacent cancer cells.

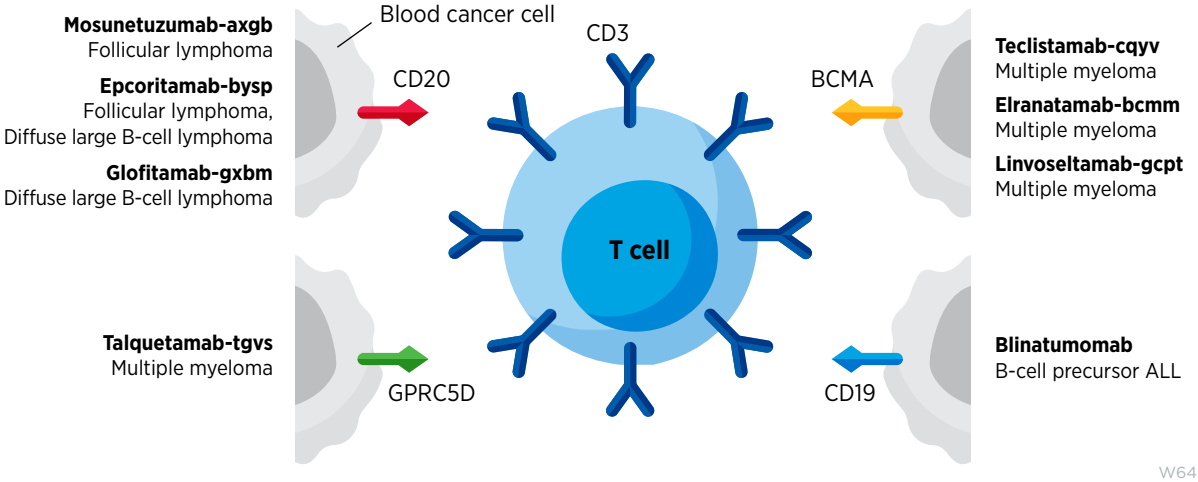
The first of these agents, blinatumomab, was approved by FDA in 2014 for treating adult patients with relapsed or refractory Philadelphia chromosome–negative B-cell precursor ALL. Blinatumomab binds to the protein CD19 on the surface of ALL cells and the protein CD3 on the surface of immune T cells. Since its first approval in 2014, FDA has allowed blinatumomab to be used in more groups of people with B-cell ALL, including those who still have small amounts of cancer left after treatment and even for those who are in remission and have no trace of their disease.

One example is the expanded approval of blinatumomab in 2017 for treating children whose ALL has returned following at least one course of treatment. FDA's decision was based on clinical studies showing that in children, AYAs, and adults with B-cell ALL that had relapsed or is not responding to therapy, treatment with blinatumomab led to better outcomes and fewer side effects compared to chemotherapy alone (782–784). Moreover, research has shown that even patients who have responded extremely well to chemotherapy and have no trace of ALL, live longer when blinatumomab is added to their maintenance treatment (785).

Another key finding was that the addition of blinatumomab to chemotherapy was highly effective for infants with newly diagnosed ALL with certain genetic alterations known as *KMT2A* rearrangement, a disease historically associated with poor outcomes (786).

Ongoing research is exploring the effectiveness of blinatumomab in combination with other therapeutics as well as in earlier stages of the disease, and even as the initial treatment for certain patients with B-cell ALL. In this regard, a large NCI-supported study of more than 1,400 children newly diagnosed with B-cell ALL, who were considered at lower risk for cancer coming back, showed that those who received

FDA-approved BiTEs in Blood Cancers



blinatumomab along with standard chemotherapy had better outcomes. After about two and a half years, 96 percent of children who received the combination treatment remained cancer-free, compared to 88 percent who received only chemotherapy (787).

Four of the FDA-approved BiTEs are for the treatment of patients with multiple myeloma, a disease that remains incurable and primarily affects older adults. In recent years, the development and FDA approval of new classes of therapeutics—including proteasome inhibitors like bortezomib and carfilzomib, immunomodulatory agents like lenalidomide and pomalidomide (Pomalyst), and immunotherapeutics like daratumumab (Darzalex) (see **Flagging Blood Cancer Cells for Destruction by the Immune System**, p. 169)—have improved outcomes for patients. Despite these advances, many patients who initially respond to these new therapies eventually experience relapses due to the development of treatment resistance.

Research has shown that the proteins GPRC5D and BCMA are highly expressed on the surface of most multiple myeloma cells. The BiTEs approved for multiple myeloma—linvoseltamab-gcpt, teclistamab- cqyv and elranatamab-bcmm, which target BCMA, and talquetamab-tgvs, which targets GPRC5D—have all demonstrated the ability to induce deep and durable responses in patients who have exhausted several prior treatments and have limited remaining options (1,177,788). Notably, in addition to disease control, many patients also experienced improvements in symptoms and quality of life.

Ongoing investigations are aimed at using these agents more effectively to further improve outcomes for more patients with multiple myeloma. For instance, researchers are evaluating the use of BiTEs earlier in the treatment course as well as combinations of BiTEs with other therapies (789). As one example, teclistamab-cqyv is being evaluated in combination with daratumumab and lenalidomide, with early data showing that nearly 90 percent of patients respond to the treatment (790). Researchers are also working to overcome resistance to the currently used BiTEs in multiple myeloma, which can occur when myeloma cells reduce the levels of or alter the structure of BCMA or GPRC5D—proteins that these therapies are designed to target (791). To address this issue, ongoing studies are evaluating dual-targeting approaches, such as combining teclistamab-cqyv and talquetamab-tgvs, to reduce the likelihood of treatment resistance (792).

The other three BiTEs approved by FDA for blood cancers are for the treatment of two different forms of NHL that arise in immune cells called B cells, FL and DLBCL. FL is a slow-growing cancer but can eventually progress to become a fatal disease, while DLBCL is an aggressive subtype that can be rapidly fatal without effective intervention. For patients who experience relapse after standard treatments such as chemotherapy and CAR T-cell therapy, therapeutic options have been limited. For FL and DLBCL, BiTEs have emerged as a transformative new treatment that redirects the immune system to eradicate cancer. By binding to the proteins CD3 on T cells and CD20 on malignant B cells, BiTEs enable targeted killing of cancer cells.

Several BiTEs have now received FDA approval for treating relapsed or refractory FL and DLBCL. Mosunetuzumab-axgb (Lunsumio) and epcoritamab-bysp (Epkinly) were approved for FL based on results from clinical studies in which 80 percent of patients saw their cancer shrink and 60 percent had

no signs of cancer after treatment (789). Longer follow-up showed a median duration of response to mosunetuzumab-axgb of 36 months, indicating durable benefit for patients who responded to the BiTE (793).

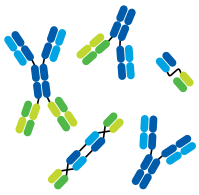
For people with aggressive DLBCL, both epcoritamab-bysp and glofitamab-gxbm (Columvi) are now approved by FDA (789). Epcoritamab-bysp helped nearly two out of three patients who received the treatment, and some responses lasted more than 2 years. Follow-up studies have underscored the long-term benefit of epcoritamab-bysp across subgroups of patients, including those with difficult-to-treat disease and poor prognosis (794). Glofitamab-gxbm has also shown strong benefits, helping over half of patients, with many seeing complete remission that lasted more than a year and a half.

BiTEs are one of the most rapidly growing therapeutic areas in cancer and are providing new hope for many patients who have few other choices remaining. Despite its effectiveness, BiTE therapy may cause serious adverse effects. Researchers are exploring ways to mitigate the range of side effects, including infections, low blood counts, cytokine release syndrome, neurologic symptoms, and other symptoms that may be associated with these treatments, especially among patients with weaker immune systems. Another key concern is that most patients eventually relapse due to the development of treatment resistance, indicating the need for better predictors of long-term benefit and ways to manage or prevent resistance.

Ongoing research is evaluating the effectiveness of BiTEs earlier in the course of treatment and in combination with other therapies. A critical area of investigation is to determine the best sequence for using BiTEs versus CAR T-cell therapies, especially when they are both approved for the same cancer type and target the same protein (e.g., tisagenlecleucel and blinatumomab are both approved for ALL and target CD19; three out of four BiTEs and both CAR T-cell therapies approved for multiple myeloma target BCMA), since giving one treatment first may affect how well the other works later on (795).

Another area of investigation is to examine whether combining two BiTEs or using biological markers to select patients can make the treatments safer and more effective. Researchers are working to identify patient characteristics, such as T-cell functional state, that predict the best response to BiTEs. In addition, efforts are underway to engineer trispecific (ability to bind to three targets) or multispecific antibody designs. These efforts aim to expand the number of patients who can benefit from these revolutionary immunotherapeutics, further improve outcomes, reduce side effects, and ultimately help more patients live longer and better lives.

Between 2015 and 2024, **370 clinical trials**, globally, **evaluated multispecific antibodies for the treatment of blood cancers**. Of these, 42% were phase I, 48% were phase II, and 10% were phase III trials.



Source: (497).

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Flagging Blood Cancer Cells for Destruction by the Immune System

Before an immune cell can destroy a cancer cell, it must find it. Many therapeutic antibodies that have been approved by FDA over the past decade for treating patients with blood cancers work, at least in part, by helping immune cells find cancer cells.

Notable agents within this group of immunotherapeutics are daratumumab and elotuzumab (Empliciti), approved in 2015, and isatuximab-irfc (Sarclisa), approved in 2020, for treating patients with multiple myeloma that has progressed despite treatment with several other therapeutics.

Both daratumumab and isatuximab-irfc work by attaching to a protein called CD38, which is found at high levels on the surface of myeloma cells. This attachment has several effects on the myeloma cells, most notably flagging them for immune cells, which upon attaching to another part of daratumumab are triggered to destroy the myeloma cells.

Elotuzumab attaches to SLAM7F, another protein found at high levels on the surface of myeloma cells. This protein is also found at high levels on immune cells called natural killer (NK) cells. Elotuzumab has distinct effects on myeloma cells and NK cells after attaching to SLAM7F on their surfaces, thus providing a two-pronged attack on multiple myeloma. It directly activates NK cells, enhancing their ability to kill myeloma cells, and it flags myeloma cells for a number of immune cell types, which once directed to the myeloma cells, attack and destroy them.

Since its initial approval, daratumumab has been evaluated in many additional studies including in combination with a variety of molecularly targeted therapeutics and immunotherapeutics among patients with newly diagnosed as well as relapsed or refractory multiple myeloma. Data from these studies have confirmed the added benefits of daratumumab combinations in delaying disease progression and even increasing overall survival for patients (796,797). Based on its transformative impact on patient outcomes, FDA has expanded the use of daratumumab in many additional settings, including as the initial treatment for multiple myeloma. Additionally, researchers are evaluating whether daratumumab can prevent the progression of smoldering

Transforming Multiple Myeloma: A Decade of FDA-approved Immunotherapies

2015 **daratumumab**
CD38-targeted antibody

elotuzumab
SLAM7F-targeted antibody

2020 **isatuximab-irfc**
CD38-targeted antibody

2021 **idecabtagene vicleucel**
BCMA-targeted CAR T-cell therapy

2022 **ciltacabtagene autoleucel**
BCMA-targeted CAR T-cell therapy

teclistamab-cqyv
BCMA- and CD3-targeted bispecific T-cell engager

2023 **talquetamab-tgvs**
GPRC5D- and CD3-targeted bispecific T-cell engager

elranatamab-bcmm
BCMA- and CD3-targeted bispecific T-cell engager

2025 **linvoseltamab-gcpt**
BCMA- and CD3-targeted bispecific T-cell engager

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multiple myeloma, a precursor disease of multiple myeloma for which no treatments are currently approved (see **Intercepting Precancerous Conditions in Blood Cancers**, p. 171) (798).

Most recently, in 2024, FDA approved daratumumab as well as isatuximab-irfc in combination with a standard initial treatment (bortezomib, lenalidomide, and dexamethasone) for patients with newly diagnosed multiple myeloma. These approvals reflect how scientifically informed combination therapies are improving patient outcomes at the clinic.

The 2024 approval of daratumumab was based on a clinical trial in which adding daratumumab to the standard regimen that includes bortezomib, lenalidomide, and dexamethasone (VRd regimen) led to deeper and more durable responses, with 84 percent of patients remaining progression-free at four years compared to 68 percent for those receiving the standard regimen (799). Additionally, patients in the daratumumab group were more likely to have no detectable cancer in their bone marrow, which is known as being minimal residual disease (MRD)–negative, than those who received standard therapy.

The approval of isatuximab was based on a study which showed that adding isatuximab to the standard VRd regimen led to significantly better outcomes, with 63 percent of patients progression-free at nearly five years, compared to 45 percent treated with VRd alone. More patients receiving isatuximab achieved complete responses and sustained MRD negativity, compared to the standard treatment group (799,800). Researchers have further demonstrated that patients who achieve MRD negativity after treatment with an isatuximab-containing regimen do not benefit from subsequent stem cell transplantation and can safely avoid the risks and side effects of a transplant (801).

The rapid development of multiple effective immunotherapies for multiple myeloma has also led to new research questions for health care providers, such as determining the best combinations and optimal sequences of treatment for individual patients and understanding whether these therapies need to be given continuously or if patients can take planned breaks. While combination regimens that include daratumumab are clearly more effective than those without it, comparative data are lacking, and health care providers currently rely on clinical judgment to guide treatment decisions. Researchers emphasize the need for clinical trials that conduct head-to-head comparisons of treatment combinations and evaluate optimal sequencing and duration of therapy to better guide future clinical practice.

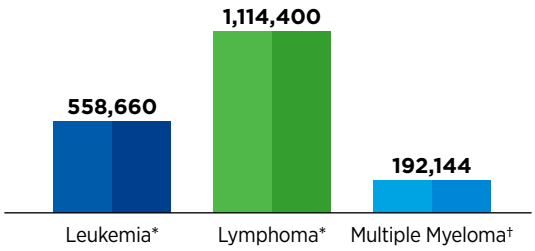
Two additional immunotherapeutics approved in the past decade that work by flagging cancer cells for destruction by the immune system are mogamulizumab-kpkc (Poteligeo) and tafasitamab-cxix (Monjuvi). Mogamulizumab-kpkc was approved in 2018 for treating CTCL. It is an antibody that targets CCR4, a protein present on certain cancerous T cells, helping the immune system destroy them. Tafasitamab-cxix was approved in 2020 for relapsed or refractory DLBCL. It targets CD19 on B cells and boosts the immune attack on cancer cells. In June 2025, FDA expanded the use of tafasitamab-cxix for patients with relapsed or refractory follicular lymphoma.

Taken together, the numerous approaches and therapeutics outlined in the previous sections highlight the transformative role of immunotherapy in reshaping the treatment landscape and improving outcomes for patients with blood cancers.

Supporting Survivorship

Thanks to the rapid pace of progress in precision early detection, prevention, diagnostics, and medicine, there are over 1.6 million survivors with a diagnosis of blood cancer living in the United States as of January 2025 (9).

Number of Blood Cancer Survivors in the United States



* Numbers as of January 1, 2025.
† Numbers as of January 1, 2022.
Sources: (4,9).

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A person can be diagnosed with blood cancer at any age depending on the type of blood cancer, as well as a multitude of genetic, environmental, and behavioral factors that can increase the risk of developing blood cancer. Consequently, survivors of blood cancers face many of the same challenges faced by survivors of any cancer (see **Supporting Cancer Patients and Survivors**, p. 177). In addition, survivors of blood cancers also experience a uniquely complex set of long-term health challenges, many of which stem from the immunologic and physiologic toll of their disease and treatments.

Unlike solid tumors, blood cancers directly involve the immune system and its central components—bone marrow, lymphoid organs, and circulating immune cells. As a result, therapies such as toxic chemotherapy, B-cell–depleting monoclonal antibodies, bispecific T-cell engagers, and CAR T-cell therapies can leave survivors with a persistently weakened immune system (802–805). This immunosuppressed state not only increases susceptibility to future infections but also often necessitates revaccination to restore protection against common pathogens (806–808).

Stem cell transplantation is a common treatment for patients with blood cancers in which they receive their own blood-forming stem cells collected before the treatment (called autologous stem cell transplantation) or from a healthy donor (called allogeneic stem cell transplantation). Compounding the treatment-related challenges, survivors of blood cancers may face the burden of chronic graft-versus-host disease (GVHD), a potential complication of stem cell transplantation in which donor immune cells attack the recipient's tissues. GVHD affects approximately 40 percent of allogeneic transplant survivors, and can manifest as skin thickening, inflamed airways, dry eyes, and overwhelming fatigue (809). Survivors also face an elevated lifetime risk of secondary malignancies (810–812), cardiotoxicity (813–815), and cognitive impairments (816–819). Fatigue, among the most commonly reported and least visible effects, often persists for years after treatment ends and significantly erodes quality of life (820).

Moreover, the financial toll of survivorship is also substantial for patients with blood cancers and caregivers. Continuous surveillance, immunotherapies, and supportive care contribute to significant out-of-pocket burdens, while persistent physical and cognitive deficits can delay or prevent a return to work, further compounding economic strain (821–824).

To address these multifaceted challenges, multidisciplinary teams that bring together hematologists, infectious disease experts, cardiologists, pulmonologists, endocrinologists, rehabilitation specialists, mental health care providers, and patient navigators offer a coordinated approach to managing chronic complications and improve quality of life (825). As an example, one study that implemented financial navigators for patients with hematologic cancer and their caregivers found that the program secured an average of $2,500 in financial benefits for each participant (826). The navigators screened patients to determine if they were at an increased risk of financial toxicity and provided assistance and resources. In addition, research has shown that embedding personalized survivorship care plans in electronic health records—with automated prompts for vaccinations, screenings, and follow-ups—can help ensure continuity in care.

New Horizons in Blood Cancer Science and Medicine

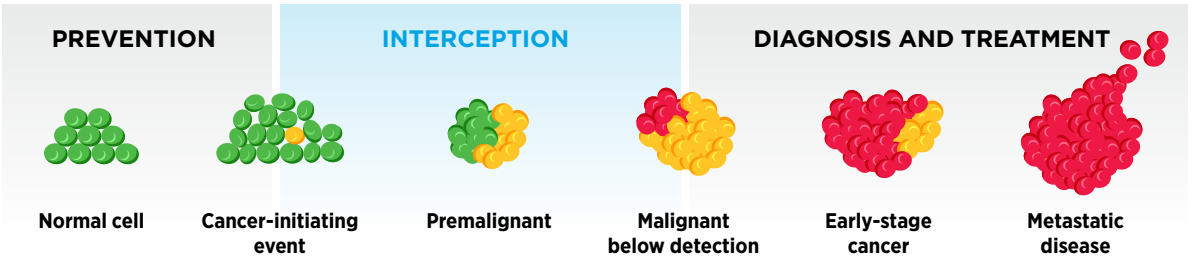
Over the past decade, advances in science and technology have transformed how hematologic malignancies are detected and diagnosed. From identifying at-risk individuals before symptoms emerge to decoding the genetic makeup of blood cancers with unprecedented precision, the field has moved rapidly toward earlier and more personalized care. This section highlights breakthroughs in genomics-based approaches that are reshaping how blood cancers are classified, monitored, and treated. Together, these innovations are poised to redefine what it means to detect, diagnose, and treat blood cancers at their earliest stages.

Intercepting Precancerous Conditions in Blood Cancers

Rapid technological advances, more effective treatments, and better ways to identify people who are at higher risk of cancer have led to a better understanding of precancers and their path to become cancer and the emergence of cancer interception (see **Figure 24**, p. 172) (827). It is an exciting area of research because treating precancerous cells at such

FIGURE 24

Intercepting Cancer



Cancer interception is a strategy focused on detecting and treating early, precancerous cell changes before they become invasive disease. Unlike traditional prevention, which aims to stop cancer from starting, interception intervenes after a first abnormal event—such as a genetic mutation—has already occurred. One example of cancer interception already in practice is the removal of precancerous polyps during routine colonoscopy.

Source: (827).

an early stage minimizes the chances of advanced cancer and improves health outcomes.

Cancer interception in hematologic malignancies focuses on identifying and targeting precancerous states—such as clonal hematopoiesis (CH), monoclonal gammopathy of undetermined significance (MGUS), and monoclonal B-cell lymphocytosis (MBL)—before they progress to become cancerous. Advances in genetic surveillance and liquid biopsy (see **Liquid Biopsy in Cancer Care**, p. 203), along with long-term follow-up studies, are enabling earlier detection of these precancerous states, setting the stage for proactive interventions tailored to the biology of each blood cancer subtype.

Precancerous Conditions That May Become Myeloid Malignancies

As people age, hematopoietic stem cells accumulate genetic alterations. In some cases, these alterations allow one group of cells to grow faster than the rest, resulting in a condition called clonal hematopoiesis (CH) (828). There are two main types. Clonal hematopoiesis of indeterminate potential (CHIP) involves genetic changes but no symptoms, and clonal cytopenia of undetermined significance (CCUS) is characterized by low blood counts (cytopenias) that cannot be otherwise explained (828). CH is especially common among older adults; about 10 percent to 20 percent of people over age 70 have it (829).

About 87 percent of CH cases involve alterations in a few key genes, for example, *DNMT3A* or *TET2*, that produce proteins involved in modifying the epigenome (see **Epigenetic Changes**, p. 40) (828,830). The remaining cases carry mutations in genes, for example, *TP53* or *JAK2*, involved in key cell processes, such as cell proliferation and growth (831). These are often found by accident when patients undergo genetic testing for unrelated medical reasons. Inherited mutations in genes, for example, *CEBPA*, *RUNX1*, and *GATA2*, can also predispose a person to CH (832).

Though many people with CH never develop serious problems, having these mutations does increase the risk of developing blood cancers, especially leukemia and myelodysplastic syndromes (828). CH is also linked to other health problems, including heart disease, stroke, and chronic inflammation (833–835). For example, people with CH caused by alterations in *TET2* or *JAK2* genes have two to four times the risk of cardiovascular disease (828).

Researchers have created risk scores, such as the clonal hematopoiesis risk score (CHRS), to help differentiate a small number of CHIP/CCUS cases that pose a higher risk of developing into myeloid cancers from a large number

The **clonal hematopoiesis risk score (CHRS)** is a composite metric that integrates the type of mutation a person has, how many cells carry that mutation, and clinical factors to **estimate a person's risk of developing blood cancer from clonal hematopoiesis**.

Source: (836).

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of cases that have minimal risk of progressing into cancer (836). Because CH is a common finding with advanced age, integrating such risk scores into clinical decision-making can help prioritize patients whose CHIP has a higher likelihood of progressing into cancer. Although there are currently no routine treatments for CHIP/CCUS, recent clinical trials are investigating potential interventions, such as anti-inflammatory drugs for high-risk CCUS, or vitamin C, which functions in concert with TET2 protein, for CCUS in which the *TET2* gene is altered (837).

Precancerous Conditions That May Become Lymphoid Malignancies

Monoclonal B-cell lymphocytosis (MBL) is a condition in which a higher-than-normal number of identical B cells originating from the same parent cell are found in the blood. People with MBL may develop other B-cell diseases, such as CLL. MBL is classified into low-count and high-count forms, depending on whether the number of identical B cells is below or above a certain threshold. High-count MBL is more likely to progress to CLL, at a rate of about 1 percent to 2 percent per year, while low-count MBL rarely progresses and is usually found incidentally in healthy older adults (838,839). Studies have shown that MBL is more common with age and in first-degree relatives of people with CLL, suggesting a genetic component. Certain infections, such as hepatitis C, may also increase the risk of developing MBL (838,840).

Researchers are working to understand how and why MBL sometimes turns into CLL. High-count MBL shares many of the same genetic features as CLL, including specific genetic alterations and abnormal B-cell receptors—proteins present on the surface of B cells. Low-count MBL has fewer of these changes and may result from normal immune responses (838,839). Advances in single-cell analysis have shown that even first waves of identical cells that originate from a single parent cell can negatively impact the immune system and blood production, especially in high-risk MBL cases (841). However, not all MBL cases follow the same path. Some remain stable for years, while others progress into CLL with significant health risks. This has raised questions about whether low- and high-count MBL are truly part of the same disease process. More long-term studies are needed to monitor how MBL behaves over time and to identify which individuals are most at risk for progression to leukemia (840).

Precancerous Conditions That May Become Multiple Myeloma

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) (842–845). MGUS is a common condition, affecting about 3 percent of people over age 50 and around 5 percent of those over the age of 70. It typically progresses very slowly, with a risk of becoming multiple myeloma of about 1 percent per year.

Researchers have created several models that help determine the risk an individual with MGUS or SMM has of developing multiple myeloma (843). These risk assessment models range from simpler 2/20/20 models to newer PANGEA models. The 2/20/20 models, developed by the International Myeloma Working Group, consider levels and ratios of certain proteins made by plasma cells, as well as the number of plasma cells in the bone marrow (846). These models are widely used in the clinic but do not offer risk assessment over time. In contrast, emerging tools like the PANGEA models also incorporate genetic alterations and other biomarkers, allowing personalized risk assessment over time (847). However, current clinical use of these models is limited because of the lack of experts needed for implementation.

Advances in genomics have revealed that early precursors of multiple myeloma exhibit fewer mutations, but progression is marked by increasing genomic alterations and the heterogeneous nature of the intermediate states (848). For example, SMM contains a mix of precancerous MGUS as well as cancerous multiple myeloma–like cell populations (843). Furthermore, mutations in genes involved in cell proliferation and DNA repair are often linked with high-risk SMM and quicker progression of the precancerous state into cancerous multiple myeloma (843,848). Studies that combine whole-genome sequencing and single-cell technologies and that follow patients with MGUS, SMM, and multiple myeloma over long periods of time are further refining our understanding of the interplay of influences inside the cell (such as genetic alterations) with those outside the cell (such as the immune system).

Multiple clinical trials are evaluating a range of therapies to intercept MGUS and SMM before they progress into multiple myeloma (see **Table 14**, p. 174). For example, trials using lenalidomide and newer T-cell–redirecting therapies, such as daratumumab, have shown promising responses in patients with high-risk SMM, including significantly lowered risk of progress to active myeloma or death, improved progression-free survival, and higher overall survival (849–851).

As intercepting precancerous hematologic conditions becomes more routine in the clinic, risk of overtreatment and concerns of toxicities associated with treatments remain. Because these precancerous conditions can take a long time to develop into cancer, long-term clinical trials are also lacking. Experts have called upon prioritizing clinical trial design that incorporates precise identification of at-risk populations, robust safety and dose optimization, and meaningful metrics that can capture early treatment benefits without compromising long-term outcomes (852). As the field evolves, the integration

TABLE 14

Selected Clinical Trials Evaluating Interception of High-risk Smoldering Multiple Myeloma Using T-cell–directing Therapies

Therapeutic(s)	Type of Therapeutic	Target Protein(s)	Clinical Trial Number(s)
ciltacabtagene autoleucel	CAR T-cell therapy	BCMA	NCT05767359
teclistamab-cqyv, daratumumab + teclistamab-cqyv or talquetamab-tgvs	Bispecific antibodies	BCMA and GPRC5D	NCT05469893; NCT06100237
linvoseltamab-gcpt	Bispecific antibody	BCMA and CD3	NCT05955508

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD3, cluster of differentiation 3; GPRC5D, G protein-coupled receptor, class C, group 5, member D.

of emerging clinical, molecular, and immune-based risk assessment tools will be essential to redefine standards for surveillance and early treatment.

Modernizing Clinical Trial Design for Blood Cancers

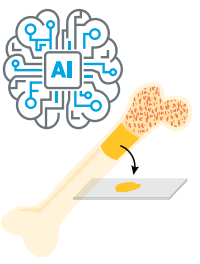
Clinical trials for hematologic malignancies have long been limited by traditional study designs that often fail to match the complexity and heterogeneity of these diseases. Standard designs—rigid phases, fixed eligibility criteria, and narrow endpoints—have slowed the pace of therapeutic innovation, particularly in rare subtypes and biologically diverse conditions, such as DLBCL, AML, and multiple myeloma. An analysis of clinical trials for hematologic cancers conducted between 2015 and 2020 found that only 21 percent of the trials were randomized, and the vast majority of randomized trials used a surrogate endpoint, such as how many patients would respond to a treatment, rather than a clinical endpoint most relevant to patients, such as overall survival (853). Furthermore, trials often struggle with underenrollment and face challenges in translating early-phase activity into long-term benefit.

To overcome these challenges, researchers are developing innovative models that simulate heterogeneity of the cancer among patients, predict trial outcomes, and inform which treatment to use before the clinical trial even starts. As one recent example, researchers integrated both heterogeneity within the cancer of a patient and heterogeneity among different patients into a model to predict how patients might respond to the treatment (854). To validate the model, researchers used real-world data from nine clinical trials evaluating the efficacy of drug combinations to treat DLBCL. The model not only accurately predicted findings of two successful trials that improved survival, but also forecasted the failure of seven trials that did not improve outcomes for patients (854). Such predictive models could make future trials more efficient, accurately predict which new drug combinations are most likely to work, and increase the chances of finding treatments that cure DLBCL, as well as other blood cancers (855).

In parallel, the clinical trial community is increasingly embracing adaptive clinical trials (see **Sidebar 28**, p. 91). For example, large trial networks like Beat AML and MyeloMATCH (see **Sidebar 47**, p. 175) in the United States are organized around treating patients based on the molecular features of their blood cancer, and allowing for quick clinical decisions to match patients with therapies based on rapid genomic profiling (857). Recent findings from the Beat AML trial show that 48 percent of AML patients above the age of 60—the age group that has a high risk of an AML diagnosis but limited treatment options available—carry a mutation that is potentially targetable for treatment (858). These collaborative trials accelerate progress against cancer by reducing duplicated efforts and increasing the likelihood of meaningful outcomes for patients with rare subtypes of cancer.

Similar efforts, such as the HARMONY Alliance in Europe, are establishing integrated data resources for blood cancers, enabling continuous learning across trials through real-world data sharing, profiling of a patient's tumor characteristics, and grouping of patients based on their tumor's characteristics to test specific treatments (859). Researchers are also introducing

A **machine learning model** predicted alterations in the *ASXL1* gene from bone marrow slide images with high accuracy, and the **prediction strongly matched the actual mutation levels**.



Source: (864).

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SIDEBAR 47

MyeloMATCH Precision Medicine Trials: A New Era in Blood Cancer Treatment

MyeloMATCH (**Myelo**id Malignancies **M**olecular **A**nalysis for **T**herapy **CH**oice) is a group of groundbreaking clinical trials designed to bring personalized medicine to adults newly diagnosed with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). Launched in May 2024 by the National Cancer Institute, myeloMATCH aims to recruit >5,000 patients across hundreds of sites in the United States and Canada.

MyeloMATCH uses the genetic profile of the disease to match patients with treatments:

Unlike traditional "one-size-fits-all" approaches, myeloMATCH uses the genetic profile of the disease to match patients with treatments tailored to the biology of their cancer.

At diagnosis, a blood or bone marrow sample is tested using a fast, high-precision genomic assay to find key genetic changes (e.g., mutations in *FLT3*, *IDH2*, *TP53* genes).

Results are returned in 2 to 3 days. If there is a match with the available treatment, patients are enrolled in a targeted treatment trial that fits their unique disease.

MyeloMATCH follows patients through every stage of care in a tiered approach:

- **TIER 1 TRIALS** offer newly diagnosed patients initial treatment to significantly reduce the disease burden.
- **TIER 2 TRIALS** treat patients who have minimal residual disease after initial treatment.
- **TIER 3 TRIALS** offer consolidation therapy—treatment that is given to kill any cancer cells that may be left.
- **TIER 4 TRIALS** treat progressively lower levels of minimal residual disease that may remain after consolidation.

As of June 30, 2025, six trials are open under the umbrella of myeloMATCH, testing molecularly targeted therapies in matched patients with AML and/or MDS.

Source: (856).

improvements to adaptive clinical trials, such as stopping the trial early if a drug is not working or accelerating patient recruitment if a drug is showing promise (860,861). Such trials are being piloted in acute leukemia and lymphoid malignancies, in which cancer spreads rapidly, so the time to decide on the right treatment is short. Quick treatment decisions are also pivotal because of the heterogeneous nature of these malignancies, which can render treatments ineffective in a short time because of the development of resistance (862,863).

Another encouraging development is the growing use of molecular features of the tumor to identify subtypes within a cancer and artificial intelligence–driven models to differentiate tumors within and among patients and guide how patients are grouped in clinical trials, especially for combination therapies. As one example, strong evidence indicates that near lack of minimal residual disease (MRD, also called measurable residual disease)—when a very small number of cancer cells remain in the body during or after treatment—can be used as a regulatory endpoint in multiple myeloma clinical trials (865).

For example, overall response rates are now routinely exceeding 90 percent in multiple myeloma clinical trials, and the median progression-free survival (see **Sidebar 32**, p. 101) is approaching 5 years in newly diagnosed patients. While these improvements in patient outcomes reflect rapid advances against the disease, they have rendered traditional endpoints like overall response rate (see **Sidebar 32**, p. 101) less effective for timely drug evaluation (865), necessitating the use of other endpoints, such as the MRD status. An analysis of data from over 13,000 patients across more than 20 trials shows that patients who were MRD-negative had improved overall survival (866,867). Following this evidence, in April 2024, FDA unanimously endorsed MRD negativity as an early endpoint that is reasonably likely to predict clinical benefit, paving the way for accelerated drug approvals in multiple myeloma (865). This milestone also

Patients with CLL require continuous treatment throughout their life. A recent clinical trial showed that **MRD-guided therapy allowed about half of the patients with CLL to stop receiving treatment by year 2** and **over two-thirds by year 4**, and improved their overall survival.

Source: (868).

W70

reflects a successful collaboration between academia, industry, and regulators, and offers a blueprint for validating intermediate endpoints in other hematologic cancers.

Two recent studies showed that using MRD status can help tailor therapy in multiple myeloma and potentially avoid unnecessary stem cell transplants. Patients who responded well to a four-drug combination—including isatuximab, carfilzomib, lenalidomide, and dexamethasone—did just as well continuing on medication as those who went on to transplant (869). The same regimen also led to high rates of deep remission with manageable side effects in a broader group of patients (801). These results support a more individualized, evidence-based approach to using drug combinations in early treatment.

Clinical trials for blood cancers are shifting from rigid, inefficient designs to flexible, data-driven systems. Tools like simulation modeling, adaptive trial structures, and biomarker-guided enrollment are reshaping how treatments are tested. This is especially critical for curable diseases like pediatric leukemias, in which smarter trial design can accelerate access to lifesaving therapies. While hurdles remain, the field is clearly moving toward faster, more precise, and patient-centered discovery.

Supporting Cancer Patients and Survivors

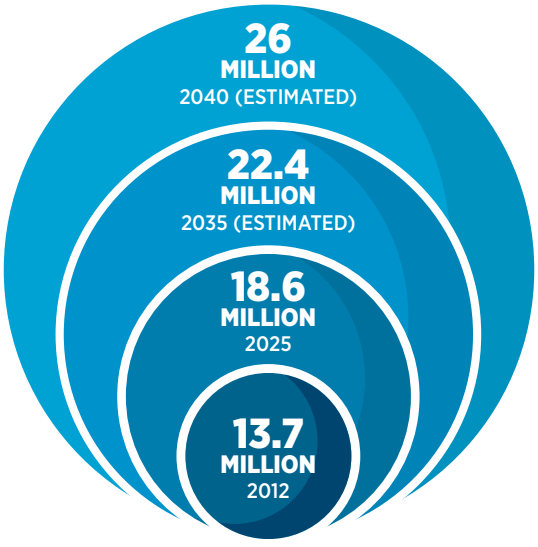
IN THIS SECTION, YOU WILL LEARN:

- As of January 1, 2025, there were an estimated 18.6 million people living with a history of a cancer diagnosis in the United States.
- Cancer patients and survivors face a multitude of physical, emotional, and financial challenges because of their cancer and treatment.
- Eating a healthy diet, reducing alcohol consumption and tobacco use, and exercising can improve the survivorship experience and cancer outcomes.
- Caregivers of patients with cancer can face the same negative health and social consequences as the family members and loved ones they care for.

According to the National Cancer Institute (NCI), a person is considered a cancer survivor from the time of cancer diagnosis through the balance of the person's life. Each person diagnosed with cancer has a unique experience ranging from successful treatment and living cancer-free for the remainder of life to experiencing varying degrees of side effects to a subsequent cancer diagnosis with the same or a different type of cancer.

Unprecedented advances in cancer treatments over the past decade have led to more patients living longer and fuller lives after a cancer diagnosis. As of January 1, 2025, more than 18.6 million adults and children with a history of cancer were living in the United States (US), representing 5.5 percent of the population (9). This reflects a substantial increase since the release of the first *AACR Cancer Progress Report* in 2011, when there were an estimated 12 million cancer survivors in the United States. Importantly, most cancer survivors today are living many years beyond their initial diagnosis. In 2025, nearly 50 percent of cancer survivors in the United States had lived 10 or more years since their diagnosis and 22 percent had lived 20 or more years (9). Looking ahead, the number of survivors is projected to exceed 22 million by 2035 and reach 26 million by 2040 (9,10).

Number of Cancer Survivors in the United States



Sources: (9,10).

W71

As more people are living longer and fuller lives after a cancer diagnosis, greater understanding of survivorship experiences is needed. These experiences include the physical, psychosocial, and economic adversities caused by a cancer diagnosis. Cancer survivors are also at risk for late effects or secondary health problems due to their cancer treatments and therefore require long-term follow-up care.

A diagnosis of cancer also impacts friends, family members, and other caregivers, who are often the main support network for the survivor. As a result, survivorship research, support, and care must extend beyond the cancer patient and survivor to include individuals who make up the support structure. The following sections highlight the challenges faced by cancer survivors and their support network, strategies to improve survival and quality of life, and approaches that have been shown to deliver care most effectively.

Addressing the Challenges Faced by Survivors

Depending on the type and stage of cancer, as well as the age at which an individual is diagnosed, cancer survivorship can encompass a wide range of unique experiences of living with, through, and beyond cancer (see **Sidebar 48**, p. 179). Physical, psychosocial, and financial stresses can deprive individuals diagnosed with cancer of meaningful life experiences regardless of which phase of survivorship they are experiencing. These challenges can also disrupt the lives of family members, friends, and other caregivers. It is important to note that the challenges discussed here are interrelated and may collectively contribute to the burden of cancer faced by cancer patients and survivors. For example, limited physical mobility because of cancer treatment and/or difficulties paying for medical bills can lead to distress and/or depression.

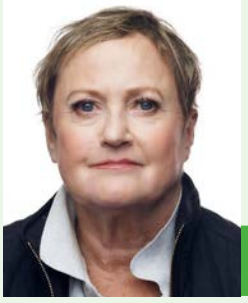
Physical Challenges

Survivors can experience a wide range of short- and long-term symptoms caused by cancer and/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, the development of long-term side effects such as heart damage (cardiotoxicity), lung damage, loss of bone density, and cognitive decline is becoming more common and demands a greater understanding to reduce or manage these conditions (see **Sidebar 48**, p. 179).

Adult survivors in the United States experience higher rates of physical disability compared to those without a history of cancer. According to a recent study, cancer survivors were 21 percent more likely to report a mobility disability (i.e., difficulty walking or climbing stairs) and 19 percent more likely to report a self-care disability (i.e., difficulty dressing or bathing), compared to those without a history of cancer (870). These functional limitations were more common among survivors who were undergoing active treatment, those who belonged to racial and ethnic minorities, and those with comorbidities or lower socioeconomic status.

A major concern for cancer survivors is the risk of recurrence or the development of a new, biologically distinct, second cancer. The likelihood of recurrence or a second cancer diagnosis is influenced by a variety of factors, including the type and stage of the initial cancer, treatments received, genetic predisposition, lifestyle behaviors (e.g., smoking), obesity, and socioeconomic status (871). Compared with the general population, cancer survivors face an estimated 16 percent increased risk of developing a second primary cancer (872,873). This risk is particularly elevated among individuals with a history of childhood cancer, as well as adult survivors of Hodgkin lymphoma, and cancers linked to obesity and tobacco use (see **Reducing the Risk of Cancer Development**, p. 51) (874–876).

My family is closer than ever; my circle of friends is smaller.



"Even though I have experienced several long-term effects, including balance issues, two new primary cancers, and heart issues, I have been alive 11 years post my diagnosis. I didn't expect to be here. I live life intentionally and try to be in the moment. I now have 2 small grandsons. Please don't stop [or] give up in frustration over funding."

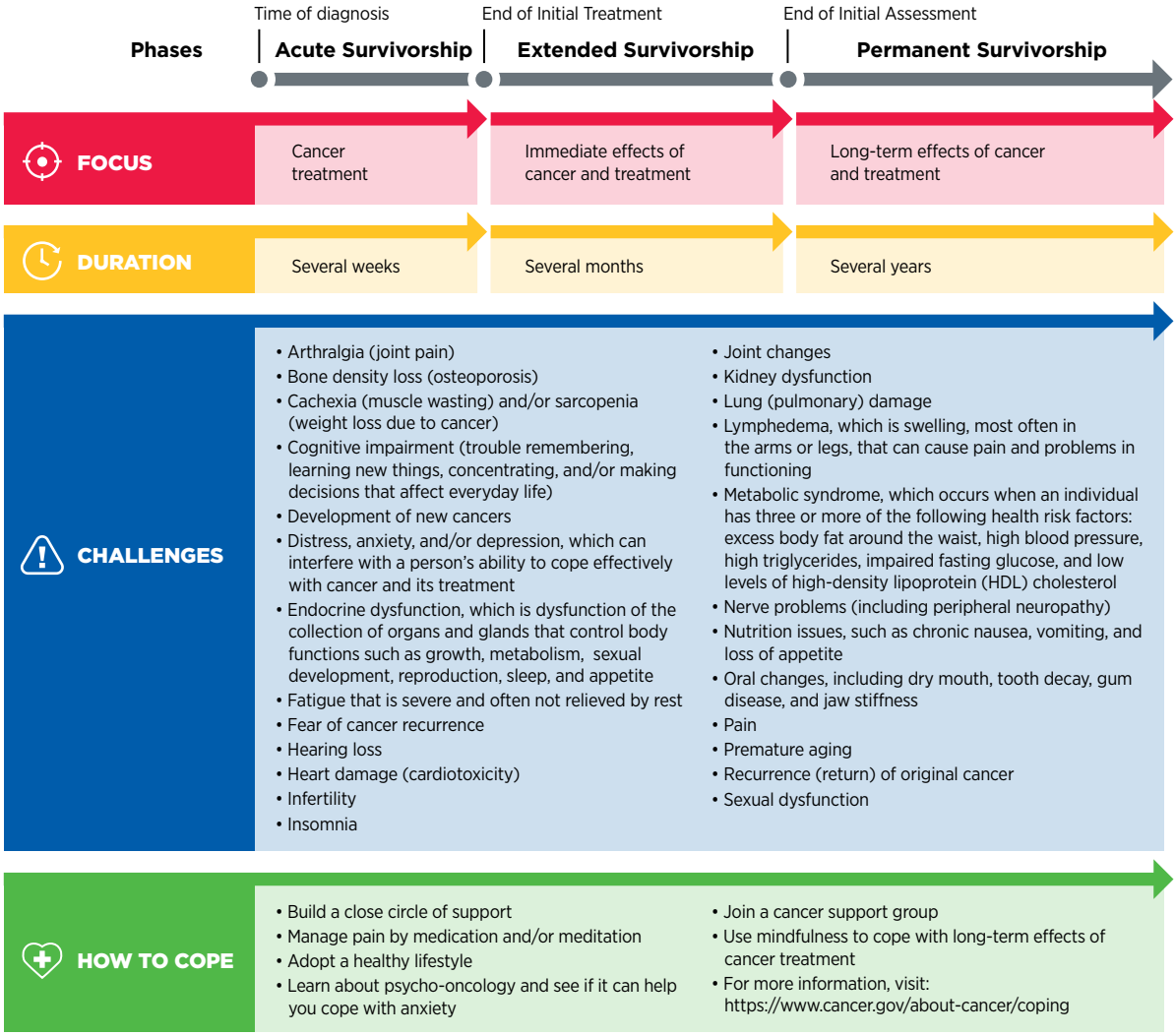
Barbara Bigelow

Scan to read Barbara's story in *AACR Cancer Progress Report 2020*

SIDEBAR 48

Phases of Cancer Survivorship

Survivorship is a continuum that can be broken down into three phases as shown below. Which phase a survivor belongs to depends on treatment received, type and stage of cancer, and the goal of care as determined by patient and care provider. It is important to note that some survivors of metastatic cancer continue to remain on active treatment for the rest of their lives to keep their cancer under control.



Although cancer survivors may face challenges, some groups are at higher risk for severe and long-term and late effects. Groups at risk include those diagnosed during childhood, adolescence, and young adulthood (from ages 0 to 39). Several organizations have established guidelines specifically for adolescent and young adult patients, including those by the National Comprehensive Cancer Network (NCCN), "Adolescents and Young Adults (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 enhance the lifelong follow-up care of individuals who were diagnosed with cancer as children, adolescents, or young adults. For more information, see **http://survivorshipguidelines.org/**.

Groups at risk also include older adults (age 65 and older). The NCCN's "Guidelines for Older Adult Oncology" address specific issues of cancer in older adults, including screening and comprehensive geriatric assessment, treatment risk and benefits, and management of complications from therapies.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and often debilitating adverse effect of cancer treatment that affects up to 85 percent of patients receiving chemotherapy. Symptoms of CIPN include numbness, tingling, burning, or electric shock–like sensations in the hands and feet, leading to functional impairment and reduced quality of life (877,878). While some symptoms resolve over time, nearly one-third of survivors experience persistent, painful neuropathy lasting 6 months or longer after treatment completion (879). A recent analysis of global data found that more than 40 percent of individuals with CIPN suffer from chronic pain (880).

Currently, treatment options for CIPN remain limited, as there are no FDA-approved medications specifically for its treatment or prevention. Duloxetine is recommended by some cancer-focused organizations for treating CIPN, but its effects are modest (881,882). However, a recent study showed that hand cooling using frozen gloves or hand compression using snug-fitting surgical gloves can reduce the risk of high-grade CIPN in breast cancer patients receiving taxane-based chemotherapy. While hand cooling and compression show promise for mitigating CIPN, more research is needed to validate these findings and determine their effectiveness across broader patient populations (883).

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. It 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 (884,885). Despite its severity, there are currently no FDA-approved treatments for cachexia. However, emerging research has provided important insights into the biological mechanisms underlying the condition and opened the door to potential therapies.

A recent clinical trial found that ponsegromab, a drug designed to block a protein linked to weight loss in cancer, significantly improved body weight, appetite, and physical activity in patients with advanced cancer (886). In addition, new evidence has shown that inflammation-related changes in the brain may play a central role in fatigue and loss of motivation often seen in patients with cachexia. Specifically, researchers found that elevated levels of the inflammatory molecule interleukin-6 can disrupt brain functions involved in motivation and energy and leading to symptoms like apathy and fatigue (887). These findings suggest that targeting inflammation in the brain may improve quality of life for patients living with cachexia.

Cancer-related cognitive impairment (CRCI), often referred to as "chemo brain," includes difficulties with memory, attention, response time, and executive function that can occur before, during, or after cancer treatment. According to a recent analysis, nearly 70 percent of cancer patients reported cognitive symptoms of any severity, and more than 30 percent reported moderate to severe cognitive difficulties. Furthermore, cognitive difficulties were strongly associated with fatigue, depression, anxiety, and other debilitating symptoms (888). CRCI is often considered a consequence of psychological distress related to cancer or its treatment. Emerging evidence suggests that CRCI may contribute to the development and persistence of various psychiatric conditions, including mood or anxiety disorders (889).

Immune checkpoint inhibitors (ICIs) are a form of immunotherapy that are increasingly used to treat a wide range of cancers (see **Releasing the Brakes on the Immune System**, p. 128). 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). These irAEs result from overactivation of the immune system and can affect any organ system. A recent analysis found that irAEs occur in approximately 40 percent of patients receiving ICI therapy, with commonly affected systems including the skin, endocrine organs, gastrointestinal tract, lungs, heart, and kidneys (625). IrAEs can occur shortly after treatment begins or even months to years after treatment initiation (890). While many irAEs are mild and manageable, others, such as myocarditis (inflammation of the heart), can be severe or life-threatening and may require treatment discontinuation (891). With the increased use of ICIs leading to long-term survival, a better understanding of their long-term and late effects is necessary.

Psychosocial Challenges

A cancer diagnosis can pose serious challenges to an individual's mental and emotional well-being. Survivors commonly face a range of psychological challenges, including anxiety, fear of recurrence, uncertainty about the future, difficulty resuming work or daily routines, changes in relationships, and social isolation (892).

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 (893).

Survivors are particularly vulnerable to emotional distress, especially in the early years following diagnosis. Many report concerns about the physical symptoms of cancer and its treatment, their emotional well-being, communication with the care team, as well as challenges about intimacy and relationships (894). Anxiety and depression are highly

prevalent among cancer survivors, who also face a greater risk of suicide than the general population (895). Encouragingly, a recent analysis found that suicide rates among individuals with cancer have declined steadily over the past several decades, with the largest decrease occurring within the past decade (896). The decline in suicide deaths among survivors may be attributable to advances in cancer treatments, increased availability and integration of psychosocial support and palliative care services, and more effective management of cancer-related symptoms and distress. However, these trends have not been uniform across all groups, as suicide rates among adolescents and young adults (AYAs) have increased in recent years (897).

Financial Challenges

Financial toxicity, the economic hardship resulting from cancer diagnosis and treatment, remains one of the most pressing challenges facing cancer survivors today. One analysis found that more than half (56 percent) of individuals with cancer experience catastrophic health expenditures, defined as out-of-pocket medical costs that exceed a substantial portion of household income (898). These financial burdens often persist for years after treatment ends, significantly impacting long-term survivorship.

Many survivors face ongoing out-of-pocket expenses for follow-up care, prescription medications, and medical equipment. A recent analysis found that US cancer survivors incur an average of $644 annually in out-of-pocket expenses for medical services, such as prescription drugs, medical equipment, outpatient care, occupational therapy, hospitalizations, and other related costs (899). These costs are compounded by income loss, reduced work capacity, and difficulty returning to employment. According to a recent survey of long-term survivors, 75 percent reported income loss and/or extra expenses. The percentage of respondents who said they were unable to make ends meet increased from 2 percent before diagnosis to 13 percent after diagnosis (900).

The financial burden of cancer is not experienced equally; certain groups are disproportionately affected. A recent study found that cancer survivors from lower-wealth households incurred higher financial debt and refinanced their homes more often compared with those without cancer (901). Another study found that survivors residing in socioeconomically disadvantaged communities were more likely to report financial hardship, regardless of insurance status (902).

Cancer-related financial hardship is associated with numerous adverse health consequences, including delayed or foregone care, decreased adherence to medications, poorer mental health, and higher mortality risk (903). In response, oncology practices are increasingly implementing screening processes to identify financial distress and unmet social needs. However, many practices lack the capacity to adequately address patients' financial needs. A recent survey of US community oncology practices found that while most practices had a financial screening process, only half had a financial navigator dedicated to assisting cancer patients. Notably, practices serving higher proportions of racial and ethnic minority patients were less likely to screen for financial concerns and less likely to have a financial navigator (904).

One promising approach to address these challenges is the Financial Toxicity Tumor Board (FTTB), first implemented at a large health care system in 2019 (905). Modeled after traditional tumor boards—which convene multidisciplinary teams of physicians and specialists to collaboratively review complex cancer cases—the FTTB brings together clinical, administrative, and supportive services to identify and resolve financial barriers to care. The FTTB includes a pharmacy-led patient assistance program, which systematically evaluates patients for eligibility in copay assistance and free drug programs, helping to reduce or eliminate out-of-pocket costs for cancer treatment. Over its first 5 years, the FTTB resolved 94 percent of cases presented and facilitated more than $400 million in patient financial assistance through its pharmacy-based program (906). Given its success, the FTTB offers a replicable model that can be adapted by other cancer centers to reduce financial hardship and improve equity in cancer care.

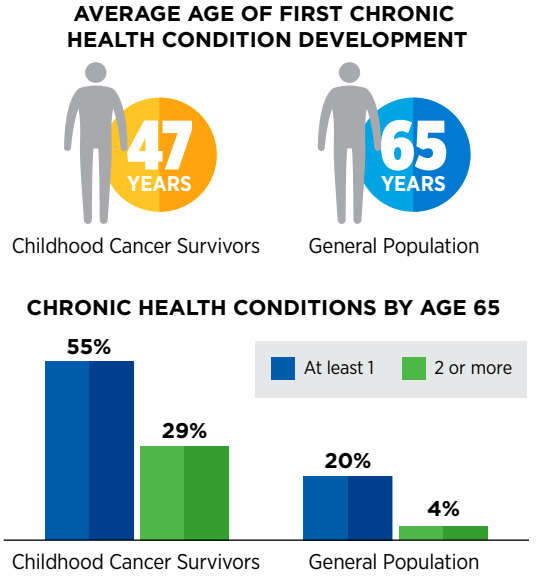
Addressing the Unique Challenges Faced by Vulnerable Populations

Challenges Faced by Children

In 2025, an estimated 9,950 US children under the age of 15 will be diagnosed with cancer. Thanks to advances in treatment, the 5-year survival rate for children diagnosed with cancer now exceeds 85 percent (2,9). This is a marked improvement compared to the mid-1970s, when only 58 percent of children lived beyond 5 years after a cancer diagnosis. Because childhood cancer survivors are diagnosed at a young age, they live longer after diagnosis than an adult who has been diagnosed with cancer.

The type and severity of long-term and late effects experienced by childhood cancer survivors depend on several factors, including the cancer type and stage at diagnosis, the specific type of treatment and doses received, and the survivor's age and overall health at the time of treatment. Among these late effects, the development of new, secondary cancers is of particular concern (872). For example, childhood cancer survivors are more than twice as likely to develop melanoma in adulthood compared to individuals without a cancer history (907).

Chronic Health Conditions in Childhood Cancer Survivors



Source: (908).

W72

Air pollution is a well-established environmental hazard linked to a range of adverse health outcomes in children, including respiratory infections, asthma, and preterm birth. Fine particulate matter (PM2.5) is especially harmful and has been associated with increased mortality in adults with cancer. Emerging evidence suggests that children and adolescents with cancer may also be vulnerable to the harmful effects of air pollution.

- In children and adolescents diagnosed with cancer, **those who lived in areas where air pollution exceeded the EPA standard** (PM2.5 ≥12 μg/m^3) faced a **6% higher risk of death** compared to those in less polluted areas.
- **More than 90%** of children and adolescents with cancer in the US **lived in areas where PM2.5 levels exceeded the World Health Organization's recommended limit** of 5 μg/m^3.

Source: (913–915).

W73

Survivors of childhood cancers are also at an increased risk of developing chronic, age-related health conditions earlier in life. These include cardiovascular disease, stroke, and other cancers. Some of these risks are influenced by inherited genetic mutations and by treatment-related changes to how genes function over time (see **Genetic Alterations**, p. 34, and **Epigenetic Changes**, p. 40) (872). A recent study estimated that childhood cancer survivors are nearly three times more likely to develop a serious age-related chronic health condition before age 65, with onset of these conditions appearing nearly 18 years earlier than in the general population (908).

Despite these risks, some long-term complications may be mitigated through protective strategies. For instance, anthracyclines, chemotherapy drugs commonly used in childhood cancer treatment, are known to increase the risk of cardiomyopathy, a disease of the heart muscle that makes it harder for the heart to pump blood effectively. However, new research shows that dexrazoxane, a cardioprotective agent given alongside anthracyclines, may help preserve heart function for up to 20 years following treatment (909).

Cancer and its treatments can also disrupt cognitive development and academic performance. A recent study found that individuals diagnosed with central nervous system tumors in early childhood experienced slower development of academic readiness skills, particularly in reading, which was associated with poorer academic outcomes later in life (910).

Childhood cancer survivors also experience lasting psychological and emotional challenges that persist well into adulthood. Fear of cancer recurrence is common. A recent study found that nearly one-third of adult survivors of childhood cancer reported elevated fear that their cancer could return or that they could develop a new cancer. This fear was strongly associated with symptoms of anxiety and depression, as well as reduced quality of life (911). Mental health concerns also include a heightened risk of suicidal ideation, or suicidal thoughts. According to one analysis, approximately 10 percent of childhood cancer survivors reported experiencing suicidal thoughts, especially during active treatment. Although childhood cancer survivors were more likely to report suicidal thoughts, their risk of suicide death was comparable to that of individuals without a cancer history (912).

Challenges Faced by Adolescents and Young Adults

AYA cancer survivors are those diagnosed between the ages of 15 and 39. An estimated 2.1 million AYA cancer survivors were living in the United States as of 2020 (874). On the basis of estimates of new cancer cases in 2025, AYAs will account for 4.2 percent of all new cases, and approximately 87 percent are expected to live 5 years or more after their diagnosis (2,916).

THE GLOBAL BURDEN OF AYA CANCER
IS PROJECTED TO INCREASE BY
ABOUT 12% FROM 2022 TO 2050

Source: (58).

W74

Many AYA survivors experience long-term and late effects, including increased risks of cardiovascular disease, metabolic disorders, cardiomyopathy, diabetes, and other chronic conditions (917,918). One study found that 40 percent of AYA cancer survivors had two or more chronic health conditions 10 years after their cancer diagnosis, compared to only 20 percent among those without a cancer history (919). Similar to childhood cancer survivors, AYA cancer survivors also have a higher risk of secondary cancers, likely due to accelerated aging (876,917,920).

Recent evidence also highlights reduced kidney function as a significant long-term risk in children and AYAs who receive certain treatments, such as chemotherapy or abdominal radiation. International guidelines now recommend routine surveillance for kidney dysfunction in children and AYA survivors to enable early detection and reduce the risk of chronic kidney disease (921).

Fertility and reproductive health remain significant concerns for AYA survivors. Depending on the cancer type and treatment regimen, risks of infertility can be high, prompting many to consider fertility preservation options before treatment (see **Sidebar 49**, p. 183). Participation in fertility preservation and the type of preservation should be decided by individuals after discussions with their health care providers. Among those who do become parents, AYA survivors face increased risks of adverse birth outcomes, including having children born preterm and/or with low birth weight (922,923).

Mental health challenges among AYA survivors are a growing area of concern. Studies consistently show that this population experiences higher rates of depression, anxiety, post-traumatic stress, and other psychiatric disorders, not only in the years immediately following diagnosis but well into adulthood (926,927). Alarmingly, suicide rates among AYA survivors have increased significantly over the past two decades, with male AYAs experiencing the steepest rise compared to survivors in other age groups (897).

For AYAs, a cancer diagnosis often coincides with a time in life when many are completing their education or establishing careers, making them particularly vulnerable to the economic disruptions caused by cancer. Nearly half of AYA blood cancer survivors report severe or high levels of financial distress, including difficulty paying bills and delaying or

SIDEBAR 49

Fertility Preservation After a Diagnosis of Cancer

A common adverse effect of cancer treatments is infertility, or the inability to conceive children. This may result from surgery on reproductive organs, radiation, or effects of cancer medications on reproductive cells and can affect both male and female AYA cancer survivors. Thus, those diagnosed with cancer should consider discussing with their health care providers whether infertility is a risk for them and, if so, whether one of the following available forms of fertility preservation is right for them.

Boys and men:

- Sperm banking
- Shielding of testes from radiation if receiving radiotherapy
- Testicular sperm extraction

Girls and women:

- Banking of ovarian tissue
- Banking of eggs
- Banking of embryos
- Surgically moving ovaries away from areas of radiotherapy
- Removing cervix but preserving uterus
- Shielding of ovaries from radiation if receiving radiotherapy

Unfortunately, fertility preservation rates are lower in survivors who are Black, poor, or living in rural areas. Currently, cancer-focused organizations have guidelines that recommend discussions of fertility preservation and sexual health as an essential part of cancer management, especially in AYA patient populations (924). Furthermore, as of June 2025, 19 states have enacted mandates requiring insurance coverage of fertility preservation for patients facing infertility due to treatments such as anticancer therapies (925). This is an increase from July 2022, when only 12 states had such mandates.

forgoing medical care due to cost (928). A recent study found that about one in six AYAs with cancer experienced moderate to severe financial difficulty persisting for several years after diagnosis, suggesting these financial hardships can be long-lasting (929). Psychosocial challenges are also common among AYA survivors, who often report difficulty maintaining friendships, returning to school or work, and achieving key developmental milestones (926).

Barriers to high-quality survivorship care and support services further compound these challenges. AYAs with cancer often face discontinuity in care as they transition between pediatric and adult-focused health care settings, neither of which is fully equipped to meet their unique developmental needs. As a result, many AYA survivors experience fragmented care, inconsistent follow-up, and poor continuity during care transitions (930). Knowledge gaps about treatment history and late-effect risks, coupled with provider unfamiliarity with risk-based surveillance protocols, further impede access to appropriate long-term care (931).

Despite considerable challenges, many AYA survivors demonstrate notable resilience, defined as the capacity to adapt and recover in the face of adversity. Interventions focused on mindfulness, stress management, and positive coping have been shown to foster psychosocial growth and improve mental health outcomes among AYA cancer survivors (932). However, access to evidence-based psychosocial care for AYAs remains limited. Childhood and AYA cancer survivors continue to need developmentally tailored survivorship care that addresses the full range of physical, psychological, financial, and social challenges they may face during and long after treatment.

Challenges Faced by Older Adults

Older adults, defined as individuals age 65 and over, currently represent 64 percent of cancer survivors in the United States, and this proportion is projected to rise to 73 percent by 2040 (933). As the population of older adults with cancer grows, so does the need to understand and address the unique physical health challenges they face.

Among older individuals with cancer, frailty is commonly recognized as an early marker of accelerated aging and is strongly associated with poor health outcomes. In a recent study of older women with breast cancer, those who experienced persistent or worsening frailty following chemotherapy were more than twice as likely to die within 5 years as those with stable or improving strength (934). Cancer treatments can also accelerate bone loss, increasing the risk of falls and fractures. In a large population-based study, older adults with cancer had significantly higher rates of major osteoporotic and hip fractures than those without cancer (935). Recent evidence indicates that the Fracture Risk Assessment Tool—a widely used and validated fraction prediction tool—can accurately predict incident fractures in individuals with cancer, providing a valuable resource for early identification of skeletal health in this population (936).

It is estimated that over 90 percent of older adults with cancer have one or more chronic conditions, such as cardiovascular disease, hypertension, obesity, and diabetes, and over 30 percent have three or more comorbidities (937,938). In the context of older survivors, pre-existing comorbidities can impact cancer treatment decisions and are associated with increased mortality and poor health outcomes (938,939). The presence of certain comorbidities also contributes to the elevated risk of developing second primary cancers. Diabetes, for example, affects nearly one-third of older breast cancer survivors and has been associated with an increased risk of developing second primary cancers of the liver, thyroid and brain (940).

The high prevalence of comorbidities among older survivors often leads to polypharmacy, defined as the regular use of five or more medications. Polypharmacy affects up to 88 percent of older adults with cancer and is associated with adverse drug reactions, treatment toxicity, functional decline, hospital admissions, increased health care expenditures, and mortality (939,941,942).

While modern treatments have improved survival, they can damage healthy tissues and disrupt biological systems, leading to the premature onset of chronic age-related diseases, such as osteoporosis, cardiac dysfunction, secondary cancers, and frailty. This earlier onset of chronic diseases is often referred to as accelerated aging (943–945). Although the concept of accelerated aging has been well-documented in childhood cancer survivors, a smaller but expanding body of literature is now focusing on older adults. Unlike younger populations, older adults are more likely to present with multiple comorbidities at diagnosis, making it challenging to disentangle the effects of aging, cancer, and its treatment on long-term health outcomes (944,946,947).

Researchers are investigating the therapeutic potential of anti-aging agents, such as senolytics and senomorphics, as clinical strategies to mitigate the effects of treatment-

induced accelerated aging among survivors. In addition to pharmacologic strategies, incorporating geriatric assessments and aging biomarkers into survivorship research and clinical care could improve early detection of accelerated aging and inform supportive care interventions tailored to the unique needs of older survivors (948,949).

Mental health conditions are common but often underrecognized in older adults with cancer. According to a recent report, one in three Medicare beneficiaries with cancer had a diagnosis of anxiety or depression (950). Social isolation also contributes to poor outcomes in this population. Research shows that older survivors experiencing severe loneliness face a 67 percent higher risk of death compared to those with little or no loneliness (951).

Older cancer survivors are also vulnerable to financial challenges, even though most have health insurance through Medicare. Among older survivors treated with surgery, more than one in four reported financial hardship, such as borrowing money, going into debt, and/or delaying care due to cost. Notably, those experiencing financial hardship were also more likely to face transportation barriers that limited access to care, highlighting the compounding challenges older survivors face in navigating both the financial and logistical burdens of survivorship (952). The high and rising costs of cancer care further exacerbate these challenges. For example, Medicare beneficiaries receiving high-cost immunotherapy are more likely to report financial hardship than those receiving lower-cost treatments (824).

Financial strain can also affect basic needs. While the overall prevalence of food insecurity among older survivors is relatively low, those who incur catastrophic health expenditures are significantly more likely to experience food insecurity. For example, older survivors who spent more than 10 percent of their household income on out-of-pocket medical costs had 1.5 times higher odds of being food insecure (953). These challenges highlight the urgent need to develop effective strategies to alleviate the financial burdens faced by older cancer survivors.

In a nationally representative study, **older cancer survivors spent an average of 28 days out of the year receiving health care outside of their homes**. This care was largely ambulatory and often delivered by non-oncologists or primary care providers.

Source: (954).

W76

Adherence to healthy lifestyle behaviors after diagnosis—including maintaining a healthy weight, engaging in regular physical activity, and following a nutritious diet—**is associated with lower cardiovascular and cancer-specific mortality** among survivors of obesity-related cancers.

Source: (367).

W77

Improving Quality of Life and Health Outcomes

Maintaining a healthy lifestyle—through regular physical activity, a healthy diet, and eliminating 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. 51). These behaviors can also improve health outcomes and quality of life for cancer survivors. In fact, a growing body of evidence shows that adopting healthy behaviors after a diagnosis of cancer can significantly improve outcomes for patients (955,956).

Participating in Physical Activity

Participating in physical activity is strongly associated with improved outcomes for cancer patients and survivors (957). According to a recent study, those who met recommended physical activity guidelines (approximately 150 to 300 minutes of moderate activity per week) had a significantly lower risk of death across 10 cancer types (see **Sidebar 18**, p. 61) (958). Notably, even modest levels of activity may offer meaningful health benefits. 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 (959).

Physical activity can improve the immune system's ability to detect and eliminate cancer cells. For example, a recent study in patients with esophageal cancer found that those who exercised while receiving chemotherapy had higher levels of immune cells within their tumors, indicating a stronger anti-tumor immune response (960). Engaging in physical activity during treatment may enhance the body's ability to fight cancer, potentially improving treatment outcomes and reducing the risk of recurrence.

Colon cancer survivors who participated in a structured, 3-year aerobic exercise program and received health education **experienced a 28% lower risk of disease recurrence, new primary cancer, or death** compared to those who received health education alone.

Source: (961).

W78

Physical activity can also help manage common treatment-related adverse effects. For example, neuromuscular training—a type of exercise that helps the nerves and muscles work together to enhance balance, coordination, and strength—has been shown to lower the incidence and severity of CIPN (962). Regular physical activity has also been associated with a reduced risk of lower extremity lymphedema among endometrial cancer survivors (963). Lymphedema is a common late effect of cancer treatment that occurs when fluid builds up in the body, leading to swelling, usually in the legs and feet.

Tailored exercise programs are proving particularly effective in managing late effects. In a recent study, a personalized, remotely monitored exercise intervention improved physical function and reduced fatigue among individuals undergoing surgery for lung cancer (964). Similarly, prostate cancer survivors who participated in a supervised aerobic and resistance training program experienced significant improvements in both sexual function and muscle strength (965).

Eating a Healthy Diet and Maintaining a Healthy Weight

Healthy diets that include fresh, minimally processed, plant-based foods are associated with improved outcomes among cancer patients and survivors. Among men with prostate cancer, adherence to a plant-based diet has been linked to reduced overall mortality, with greater benefits observed among Black survivors (967). In contrast, diets high in ultra-processed foods and added sugars have been linked to worse outcomes. Colorectal cancer survivors who consumed higher levels of ultra-processed foods had a significantly increased risk of cardiovascular disease mortality, with specific foods like ice cream linked to higher colorectal cancer–specific mortality (968). Similarly, adult survivors of childhood cancer who regularly consumed sugar-sweetened beverages faced a greater risk of accelerated aging, reflected in a higher burden of chronic health conditions (969).

Research has shown that **mind–body exercise** approaches, such as tai chi and yoga, **reduce symptoms of depression and anxiety**, especially among older survivors of cancer.

Source: (966).

W79

Food insecurity, which is 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. Moreover, survivors with food insecurity have an increased risk of all-cause mortality compared to their food-secure counterparts (970). Cancer survivors living in food deserts, or geographic areas with limited access to healthy and affordable food, face additional barriers to maintaining a healthy diet. Among cancer survivors residing in the US South, those with low socioeconomic status were more likely than higher-income individuals to live in food deserts and had to travel greater distances to access nutritious food options (971).

Promoting healthy dietary patterns can help reduce treatment-related side effects, improve quality of life, and lower mortality risk among cancer survivors. For example, older cancer survivors who participated in a year-long, home-based vegetable gardening intervention—with monthly visits from professional gardeners and regular planting and maintenance activities—significantly increased their fruit and vegetable intake and experienced improvements in physical performance and perceived health compared to survivors who did not participate (972).

Eliminating Alcohol and Tobacco Use

Smoking among cancer survivors is associated with adverse health outcomes, including increased risks of recurrence and secondary cancers, greater treatment-related complications, reduced quality of life, and higher mortality (973,974). However, 15 percent of cancer patients in the United States report being current smokers at the time of their diagnosis (196). The use of electronic cigarettes (e-cigarettes) has been on the rise in recent years, especially among younger cancer survivors (see **Reducing the Risk of Cancer Development**, p. 51). In 2017, 27 percent of cancer survivors under age 50 used e-cigarettes compared to just 8 percent among survivors age 50 or older (975). Notably, over half of survivors who currently smoke traditional cigarettes also report using e-cigarettes (976). According to one study, pain may be a contributing factor. Cancer survivors experiencing greater

In 2019, approximately **19,500 cancer deaths** in the United States were **attributable to alcohol consumption**, accounting for 3.8% of all cancer deaths.

Source: (163).

W80

pain are significantly more likely to smoke cigarettes, including e-cigarettes (977).

Given these patterns, promoting smoking cessation is critical. Quitting smoking can have immediate and long-term positive effects for cancer survivors. According to one study, individuals who stopped smoking within 6 months of a cancer diagnosis experienced significantly improved survival, gaining nearly two additional years of life compared to those who continued smoking (197).

Consumption of alcohol can lead to adverse health and treatment outcomes among cancer patients and survivors, including increased risk of cancer recurrence, new malignancies, and mortality (978). Unfortunately, 71 percent of individuals with a history of cancer report consuming alcohol. Among those who drink, 46 percent exceed the upper limits defined in the guidelines (more than 1 drink per day for women or 2 for men; see **Sidebar 19**, p. 63) and 32 percent engage in hazardous drinking (i.e., alcohol consumption that increases a person's risk of harm) (979).

Although few alcohol interventions have been developed specifically for cancer survivors, care providers should refer patients with alcohol use disorder (AUD) to evidence-based treatments, such as behavioral counseling and/or medication. Despite their availability, treatment for AUD remains underutilized among cancer patients and survivors. A recent study found that among survivors newly diagnosed with AUD, only 14 percent initiated any form of treatment and fewer than 3 percent received FDA-approved AUD medications (980). Integrating routine alcohol use screening into cancer care could significantly reduce the burden of avoidable cancer-related complications. As such, more research on intervention strategies specifically to reduce alcohol abuse in cancer survivors is warranted.

Integrating Palliative Care

Palliative care is an approach to prevent or manage the symptoms and side effects of any disease, including cancer, by addressing the physical, psychosocial, financial, and spiritual needs that arise from the disease and treatments

SIDEBAR 50

What Is Palliative Care?

Palliative care is specialized care that is focused on improving the quality of life for patients with and survivors of serious illnesses, such as cancer, and their families and caregivers. The goal of palliative care is to prevent or treat, as early as possible, the symptoms and side effects of cancer and its treatment, as well as any related psychological, social, or spiritual challenges.

Palliative care is given throughout a person's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care. Palliative care given near the end of life, after curative treatment has stopped, is often referred to as hospice care.

Palliative care can be given in addition to cancer treatment or to those with no curative treatment options. Palliative care addresses many of the challenges that can affect quality of life after a cancer diagnosis, including:

- Emotional challenges, such as anxiety and depression.
- Physical symptoms and adverse effects of the disease and its treatment, such as pain, nausea, vomiting, fatigue, difficulty sleeping, and loss of appetite.
- Practical challenges, such as navigating the health care system.
- Spiritual challenges.

Source: (12).

(see **Sidebar 50**, p. 187). Palliative care is facilitated by multidisciplinary teams of doctors, nurses, dieticians, pharmacists, therapists, spiritual leaders, and social workers, and has been shown to improve quality of life for patients, families, and caregivers (981). Importantly, palliative care is appropriate at any stage of disease and can be provided alongside curative or life-prolonging therapies.

A growing body of evidence supports the early integration of palliative care, which has been associated with better symptom

management, reduced depression and anxiety, improved coping, and better emotional well-being for both patients and families (982,983). Early palliative care can also help patients and caregivers navigate the uncertainty of modern cancer therapies, improve understanding of disease prognosis, and support care planning that aligns with patients' goals, values, and preferences (983).

Individuals living with advanced or metastatic cancer face distinct survivorship challenges that require dedicated standards of care, including integrated models that reflect the reality of living longer with an incurable disease (984,985). Early referral to specialized palliative care is recommended for this population and has been shown to enhance quality of life, improve symptom management, and increase the likelihood of discussing and documenting end-of-life preferences (986).

Despite these benefits, many patients with cancer still receive aggressive treatment near the end of life, which may not reflect their preferences, can compromise quality of life, and often contributes to emotional distress for both patients and their families. According to a recent study, nearly half of Medicare beneficiaries with advanced cancer received potentially aggressive care in the last 30 days of life, while only a minority received timely palliative care or participated in advance care planning (987). Early palliative care remains underutilized, in part due to a shortage of palliative care clinicians, underscoring the need for scalable, flexible models that expand access.

Stepped-care models are increasingly being used in oncology settings to deliver scalable, personalized care that is tailored to each survivor's level of need. In general, the stepped-care model is an adaptive treatment framework in which all patients receive a baseline level of care, and treatment intensity is adjusted over time based on clinical need, treatment response, and patient preferences (988). 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 (988).

Recent national data from Commission on Cancer (CoC)–accredited institutions further highlight the need for integrated survivorship and palliative care models. In 2021, CoC introduced Standard 4.8, which requires accredited cancer centers to establish a structured survivorship program with a designated leadership team and dedicated services for patients who have completed treatment. A survey of over 380 CoC-accredited programs found that while most institutions offer core survivorship services, such as cancer screening, nutritional counseling, and specialist referrals, services addressing sexual health, fertility, and psychosocial needs remain underutilized (989).

Adult survivorship care is typically delivered by the cancer treatment team rather than through dedicated clinics, and only a minority of patients receive these services due to low referral rates and limited patient awareness. Experts emphasize embedding survivorship care into electronic health records (EHR), automating symptom alerts, and ensuring institutional commitment to sustainable staffing and funding (990). These efforts reinforce the broader imperative to treat survivorship and palliative care as continuous, complementary components of high-quality cancer care.

Palliative Care Challenges in Low- and Middle-Income Countries (LMICs)

In a survey of 180 health care providers in LMICs:

- **50% lacked specialization** in palliative care.
- **Adherence to palliative care guidelines varied widely**, with early palliative care referrals ranging from 51% in the Americas to 0% in the Western Pacific region.
- **Key barriers** included lack of policy support, unmet educational needs, and accessibility constraints.

Source: (991).

W81

Improving Mental Health

The psychological challenges faced by survivors of cancer necessitate approaches that improve the mental well-being of this population. Several approaches can be utilized, including mind–body interventions, mental health screening, physical activity, and community engagement (966,992,993).

A recent study outlined a stepped-care model for managing fear of cancer recurrence, in which all survivors receive universal psychoeducation (e.g., general information about recurrence risk, the nature of fear of recurrence, and basic coping strategies), followed by more intensive interventions (e.g., clinician-delivered psychotherapy) for patients with moderate or severe symptoms. The model emphasizes regular screening to guide care decisions, as well as flexible delivery formats (e.g., in-person, digital, or hybrid) to accommodate diverse survivor needs and health care settings (994).

Despite the substantial distress associated with a cancer diagnosis and treatment, many survivors report experiencing personal growth or positive psychological change as a result

SIDEBAR 51

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 (932). 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, and 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 (932,996–998).

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.

of their 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 (932) (see **Sidebar 51**, p. 189). Research has shown that resilience can mitigate the negative effects of depression and enhance quality of life for individuals with cancer (995).

Psychosocial interventions that focus on enhancing resilience by teaching 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. Among AYAs with advanced cancer, resilience-focused interventions have been associated with increased hope and greater engagement in meaningful health care discussions, including those related to care preferences and goals (996). Importantly, these benefits were not only evident shortly after the intervention but were also sustained over time, suggesting a long-term impact on quality of life and mental health.

These findings underscore the importance of leveraging resilience in survivorship care. By integrating resilience-building strategies into routine oncology practice, providers can offer more holistic, patient-centered support that empowers individuals to navigate the emotional complexities of cancer with greater confidence and psychological strength.

Delivering Care to Cancer Survivors

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.

Coordinating cancer care is most effective when a designated individual or a team of people helps a cancer patient or survivor gain access to the resources they need. Patient navigators and clinical care coordinators are individuals who help cancer patients and survivors access resources more effectively (see **Sidebar 52**, p. 191). 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 (999). One such program, the Integrated Cancer Care Access 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. Research on ICCAN demonstrated that patients who received these services experienced significantly higher treatment completion rates and greater improvements in quality of life, depression, and stress compared to those receiving standard care (1000).

Survivorship care plans (SCPs) are another effective tool for improving care coordination. SCPs typically include a summary of the patient's diagnosis and treatment, follow-up care recommendations, and guidance on managing long-term effects. SCPs serve as a critical bridge between oncology and primary care settings, promoting coordinated, continuous care as survivors transition out of active treatment. Recent studies have shown that patients who receive SCPs are more likely to adhere to recommended cancer screening guidelines across a range of cancer types (1001,1002). 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, primary care providers (PCPs), and patients (1003,1004).

Recognition of the critical role that PCPs play in cancer survivorship is growing, as they are well-positioned to manage comorbidities, deliver preventive care, and support 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 (1005). 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.

Despite increasing recognition of survivorship as a distinct phase of the cancer continuum, the delivery of coordinated care remains inconsistent, and SCPs are still not routinely integrated into the standard practice (989). To address these gaps, NCI, in collaboration with the Department of Veterans Affairs and other stakeholders, recently established national standards for cancer survivorship care (1006). These national standards are intended to guide the development of comprehensive survivorship programs across diverse settings and ensure that all survivors have access to high-quality, coordinated services.

However, meeting these standards will require addressing key workforce challenges. In addition to persistent shortages of oncologists and primary care providers, there are currently no accredited training programs in cancer survivorship, limiting efforts to standardize care and prepare the next generation of providers (1007). Expanding access to survivorship services will require greater investment in training and supporting multidisciplinary care teams, including patient navigators, clinical care coordinators, and other professionals who are essential to delivering high-quality survivorship care.

Leveraging Patient Reported Outcomes

Patient reported outcomes (PROs), which are direct reports from patients about their health and daily functioning, are

SIDEBAR 52

Patient Navigation for Cancer Survivors

The first patient navigation program in the United States was designed specifically to address racial disparities in breast cancer screening and follow-up for Black women. Implementation of this program led to a 70 percent increase in 5-year survival in this group (1008). While patient navigation is recognized more frequently as a potent resource for helping cancer survivors, challenges in implementation remain.

Benefits

Patient navigation bridges a variety of gaps and addresses diverse needs across the cancer care continuum. Specifically, patient navigation:

- Improves access to screening, patient care coordination, symptom management, and follow-up care (406,999,1009).
- Reduces the cost of health care by reducing emergency room visits and missed appointments (826,1010,1011).
- Reduces financial toxicity for patients with cancer (826,1010,1012).

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 Patient Navigation Outreach and Chronic Disease Prevention Act in 2005, which provided $25 million over 5 years to develop patient navigator programs and determine if they help reduce barriers to access to care and improve health care outcomes in underserved patient populations. This act was the first of its kind in the United States.
- The Patient Protection and Affordable Care Act in 2010, which helped increase access to patient navigation programs for cancer patients and survivors.
- Additionally, the American College of Surgeons' Commission on Cancer requires all accredited organizations to have a patient navigation program. The Community Preventive Services Task Force (CPSTF) also recommends the use of patient navigation services to increase cancer screenings among historically disadvantaged racial and ethnic populations and people with lower incomes.

Challenges

Despite the benefits of patient navigators, challenges remain:

- There is often high variability in the organization and training of patient navigators in the United States. Lack of standardization can lead to different experiences for survivors.
- There is often confusion about coverage and financial benefits of patient navigator services through Medicare, Medicaid, The Indian Health Service, and private/commercial insurers.
- Patient navigation services are not well integrated into the health information system, which simplifies care coordination by improving access to patient history and health information in health care settings. This results in poor coordination and delayed information sharing among patient navigators.

increasingly recognized as essential tools in clinical trials as well as routine practice (see **Sidebar 53**, p. 192). PROs provide critical insights into symptoms, functional status, and quality of life, enabling a more comprehensive understanding of treatment tolerability and patient well-being (1013,1014).

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 integrated into clinical care with automated alerts, these systems can prompt timely interventions by health care providers (1015). Evidence from large-scale trials shows that patients engaged in regular symptom monitoring experience better clinical outcomes, including improved symptom control, better quality of life, and fewer emergency department visits and hospitalizations (1016,1017).

The integration of PROs with EHRs and real-time alert systems has proven both feasible and effective across diverse clinical

SIDEBAR 53

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.

Source: (1).

settings. In a recent clinical trial, EHR-integrated PRO systems not only supported more responsive care but also improved communication between patients and providers (1016).

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. 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 (1014).

Incorporating PROs into standard cancer care represents a meaningful step toward more patient-centered, responsive, and effective cancer care. As the evidence grows, particularly in pediatric populations, the integration of PROs should be prioritized to ensure that the patient voice is central to care delivery.

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 2020, over 53 million US adults provided care for another person (1018). Among them, an estimated four million were caring for an adult with cancer.

Caregivers are vulnerable to a range of adverse health outcomes. 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 (1019). Other studies indicate that between 15 percent and 40 percent of cancer caregivers meet criteria for clinically significant traumatic stress or depression (1020). The emotional demands of caregiving are especially challenging for spouses of cancer patients, who face elevated risks of both suicide attempt and suicide death, especially within the first year after diagnosis (1021).

Cancer survivors who also serve as caregivers face additional burdens. A national survey found that nearly one in five cancer survivors reported having caregiving responsibilities. These survivors were more than twice as likely to experience moderate to severe psychological distress as those without caregiving duties (1022).

Emerging research highlights the interdependence of patient and caregiver experiences. In a study of breast cancer patients and their primary caregivers, nearly one-third of caregivers reported symptoms of depression, and financial toxicity was strongly linked to both the caregiver depression and the patient's fear of cancer recurrence (1023). Notably, the patient's fear of recurrence also affected the caregiver's emotional well-being, underscoring the shared and interconnected nature of distress within caregiving relationships.

Moreover, caregivers often face compounding social and financial challenges that exacerbate financial and emotional strain. These include housing and food insecurity, 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 (1024). 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.

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 (1025). Efforts to increase support for cancer caregivers are urgently needed because nearly a quarter of CoC-accredited US cancer centers do not have a family caregiver program (1026).

Envisioning the Future of Cancer Science and Medicine

IN THIS SECTION, YOU WILL LEARN:

- Artificial intelligence has the potential to transform the future of cancer research and patient care by accelerating discoveries, streamlining drug development, and advancing precision oncology.
- Precision gene editing technologies may help shape the future of cancer research by enabling more advanced cancer models, discovering novel therapeutic targets, and developing more personalized treatments.
- Liquid biopsies can advance the future of cancer detection and treatment as powerful, minimally invasive tools for detecting cancer earlier and monitoring treatment response throughout the course of therapy.
- Next-generation treatments, including cancer vaccines and radiopharmaceutical therapies, could redefine the future of cancer care and offer new hope for difficult-to-treat cancers.

The pace of progress against cancer has accelerated tremendously in recent years, as underscored throughout this 15th edition and past versions of this annual report. 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.

Technological and therapeutic advances against cancer and their impact on saving and improving lives of patients with cancer are a source of great optimism for cancer researchers, including **AACR President, 2025–2026, Lillian L. Siu, MD, FAACR, FRCPC** (see p. 196).

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 10**, p. 39). For example, spatial profiling is allowing researchers to map interactions of tumor and immune cells within intact tissues, offering new insight into the tumor microenvironment (TME) and its role in treatment resistance (1027). Technologies such as organoid systems, miniature organ-like structures grown from a patient's own tumor cells, and three-dimensional (3D) tumor culture models (see **Sidebar 6**, p. 31) are advancing our understanding of the disease by more closely mimicking cancer biology and accelerating the development of more effective, personalized therapies (1028,1029). The sections below highlight some of the most promising emerging technologies in cancer research.

New Advances in 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 (ML), deep learning (DL), generative AI (GenAI), large language models (LLMs), and agentic AI, are now being applied to tasks such as analyzing histopathology images, identifying genomic alterations, and discovering new drug candidates (see **Sidebar 54**, p. 198). This section will highlight some of the ways AI is being harnessed across the cancer care continuum, including its use in accelerating basic research discoveries, improving early detection, enhancing diagnostics, streamlining drug development, and supporting clinical decision-making. It will also address the importance of ensuring AI advances are effective and accessible to all patient populations.

Accelerating Basic Research Discoveries

AI is rapidly transforming basic research by helping scientists interpret biological data and uncover molecular patterns that drive cancer development. DL models and LLMs are now being applied across foundational areas of cancer research. One emerging application for AI in basic research is its use in enhancing the clinical relevance of knowledge gained from laboratory models of cancer. For example, researchers recently developed a DL-based method that integrates transcriptomic data from cell lines, patient-derived xenografts, and patient tumors simultaneously (see **Sidebar 6**, p. 31) (1032). This approach enables researchers to identify which laboratory models most closely resemble a patient's tumors and ensure that findings from laboratory experiments are more likely to translate into meaningful clinical advances.

DL models are also advancing our ability to model gene regulation, enabling the prediction of gene expression directly from DNA sequences and aiding the interpretation of non-coding variants—genetic changes that occur outside protein-coding regions but can still affect how genes are regulated and expressed (1033). Researchers have developed a DL model that analyzes transcriptomic data from more than 50,000 tumors across 18 cancer types to uncover patterns in gene activity that reflect important differences between cancers. These patterns help link specific molecular features to immune responses, cancer subtypes, and patient outcomes (1034). As these technologies advance, their integration into cancer research will provide new insights into cancer biology and accelerate future discoveries.

Improving Detection and Diagnosis

AI-driven tools have the potential to offer faster, more accurate, and less invasive methods to detect and diagnose cancer. As one example, using over 163,000 low-dose computed tomography (CT) scans of the chest and 49 types of clinical records—such as pathology test results and demographic information—researchers recently developed an AI model to enhance lung cancer diagnosis. The model automates the analysis of 3D CT scans and integrates this information with clinical data. It assists radiologists—doctors trained to create and interpret medical images such as X-rays and CT scans—in identifying lung nodules and assessing cancer risk (1035).

Researchers have also developed a novel DL model to detect pancreatic tumors from CT images with over 94 percent accuracy, highlighting the potential for AI in identifying hard-to-detect cancers (1036). In another study, researchers using a DL model achieved more than 99 percent accuracy in diagnosing endometrial cancer from histopathologic images, showing how this approach can reduce diagnostic delays, catch cancer earlier, and improve patient outcomes (1037).

Recent advances in ML technologies are harnessing noninvasive biomarkers—measurable molecular markers found in body fluids that can signal the presence of disease or response to treatment—to improve early cancer detection. In one study, researchers used microbiome-based biomarkers (see **Microbiome**, p. 44) with ML models to improve early detection of pancreatic cancer. Using information about the microbiome from blood samples, researchers developed ML models capable of distinguishing patients with pancreatic cancer from healthy individuals with over 95 percent accuracy (1038). This represents a major advance for a cancer that is extremely difficult to detect early and has one of the highest mortality rates due to late-stage diagnosis. In another study, researchers developed an ML model to analyze samples from noninvasive blood-based liquid biopsies (see **Liquid Biopsy in Cancer Care**, p. 203) that detected gliomas across all grades with high sensitivity (1039).

Together, these examples demonstrate how AI-powered diagnostic tools are advancing earlier, less invasive detection of some of the deadliest cancers, particularly those that often go unnoticed until symptoms appear at more advanced stages. In addition to helping with early detection of difficult-to-detect cancers, AI is also accelerating improved detection of cancers for which effective screening methods already exist, such as helping read mammograms to detect breast cancer faster, more accurately, and efficiently (see **Technological Innovations Advance Cancer Screening for Early Detection**, p. 82).

Recent studies show that AI can improve how patients are classified based on their tumor's characteristics. For instance, researchers developed a DL model that accurately predicts *EGFR* and *KRAS* mutations—genetic alterations commonly associated with aggressive forms of the disease—in lung cancer from routine histology images, potentially eliminating the need for often costly conventional genetic sequencing (1040).

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Advancing Cancer Science and Medicine Through Technological Innovation and Precision Care

Lillian L. Siu, MD, FAACR, FRCPC
AACR PRESIDENT, 2025–2026
Professor, University of Toronto; Medical Oncologist, Princess Margaret Cancer Centre; Director, Phase I Clinical Trials Program; BMO Chair in Precision Cancer Genomics; University Health Network, Toronto, Ontario, Canada

Over the course of my three decades in cancer research and clinical care, I have witnessed a remarkable evolution in how we understand and treat cancer. Much of this progress has been documented in *AACR Cancer Progress Report 2025*, and the 14 prior editions. The next decade promises an even greater transformation, driven by technological advances in artificial intelligence (AI), multi-omics, and our collective commitment to translating science into better outcomes for patients.

Every breakthrough in cancer begins with basic, or fundamental, research. These studies allow us to answer the most critical questions: Why does cancer develop? Why does it grow and spread? And why do some cancers that appear identical under the microscope behave so differently? Without understanding the underlying biology, we cannot fully appreciate these differences or identify cancer's vulnerabilities.

For physician-scientists like me, the insights from basic science are invaluable. Our colleagues in the laboratory help identify the targets that drive cancer, as well as the mechanisms that lead to resistance—one of the biggest barriers to treatment success. This exchange of knowledge between basic, translational, and clinical research is vital.

Molecularly targeted therapies now allow us to home in on specific genetic alterations in cancer cells, delivering precision treatments that spare healthy tissue and reduce side effects. Immunotherapeutics, particularly immune checkpoint inhibitors, have revolutionized care for melanoma, lung, head and neck and multiple other cancers, offering the possibility of long-term survival for patients once thought to have no options.

Technological advances, such as next-generation sequencing, have dramatically lowered the cost and time needed to analyze a cancer patient's genome. We can now pinpoint not only the gene driving a cancer but even the specific variants within the driver genes, enabling highly selective treatments such as KRAS G12C inhibitors. Equally exciting is the progress in immunotherapy beyond checkpoint blockade, including bispecific antibodies, adoptive cell therapies, and therapeutic cancer vaccines.

Looking ahead, I see enormous potential in liquid biopsy technologies. By analyzing circulating tumor DNA in blood or other body fluids of patients with no symptoms of cancer, we can detect minimal residual disease long before it appears on imaging, giving us the opportunity to intervene or intercept cancer. As these technologies become more sensitive, this "needle in a haystack" detection could be a game changer for cancer early detection, prevention, and treatment monitoring.

AI is rapidly transforming cancer research and patient care. AI can enhance digital pathology, enabling the detection of histological changes indicative of cancer that are invisible to the human eye, and can revolutionize imaging interpretation for CT and MRI scans. It can also analyze vast datasets to uncover patterns that might otherwise be missed. AI can also be leveraged to match patients to clinical trials—which would be particularly impactful in trials for pediatric and rare cancers—and to design smarter, more rational treatment combinations.

Some of the groundbreaking advances in precision medicine and immunotherapy began in hematologic cancers, laying the foundation for innovations now reshaping the treatment of many other cancer types. CAR T-cell therapies and bispecific T-cell engagers have significantly improved outcomes in patients with multiple myeloma, lymphoma, and childhood B-cell acute lymphoblastic leukemia. The hematology field's long-standing expertise in measuring minimal residual disease provides valuable lessons for solid tumor oncology, underscoring the importance of cross-disciplinary learning.

The rapid pace of new drug development has been fueled by dramatic advances in clinical trial design. Once limited to rigid, sequential phases, trials are now more seamless, adaptive, and inclusive, enrolling hundreds or even thousands of patients worldwide. Globalization of research has expanded access to diverse patient populations and rare cancer subtypes, accelerating the pace of discovery. Innovative master protocol designs like basket and umbrella trials have improved efficiency, allowing us to test multiple treatments or target multiple alterations under a single protocol.

Yet challenges remain. Funding for cancer research is under threat at a time when keeping the momentum is crucial. Sustained investment in medical research ensures that we can piece together the complex puzzle of cancer and continue building the pipeline of innovations that will transform the future of patient care. If we fail to invest today, we risk slowing or even halting the progress that will save lives in the next decades.

AACR plays a vital role in sustaining this progress. Through initiatives like AACR Project GENIE®, which aggregates genomic and clinical data from more than 200,000 patients worldwide, we are enabling the discovery of treatment strategies for rare cancers and fostering global collaboration. We recognize that ensuring a stable pipeline of future cancer researchers requires investing in the workforce as early as the high school and undergraduate student levels. By offering free student membership and AACR-Undergraduate Scholar Awards, AACR aims to inspire and engage the next generation of scientists.

Scan the QR code to watch Dr. Siu's video interview.

"Cancer research is a continuum. From bench to bedside and back to the bench, technological innovations are fueling rapid advances across the continuum to detect cancer earlier and develop more precise treatments."

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Additionally, our trailblazer grants are also supporting early-stage and mid-career scientists in pursuing bold, high-risk ideas—fueling the discoveries of tomorrow.

As I look to the future, I am inspired by the pace of innovation and the dedication of the cancer research community. The technologies and treatments emerging today have the potential not only to extend life but to preserve its quality, turning cancer into a manageable condition or preventing it altogether. Together—scientists, clinicians, patients, advocates, funders, and policymakers—we can ensure that the momentum continues and that every discovery brings us closer to our shared vision: a world where fewer people develop cancer, more people are cured, and all patients live longer, healthier lives.

SIDEBAR 54

Understanding Artificial Intelligence and Its Impact on Cancer Care

Artificial intelligence (AI)

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 based on genomic, proteomic, and image data.

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.

Sources: (1030,1031).

In medulloblastoma, the most common malignant brain tumor in children, accurate molecular classification of tumors plays a critical role in guiding treatment decisions but typically requires invasive procedures and time-consuming molecular tests. In a recent study, researchers showed that ML algorithms trained on gene expression data classified medulloblastoma with high accuracy, including those with poor prognosis and high metastasis rates (1041).

In another study, researchers developed an AI model that used spatial transcriptomics to automate histologic and molecular diagnosis of central nervous system tumors. The model accurately predicted tissue histology and tumor subtypes with more than 89 percent accuracy, demonstrating its potential to precisely identify and diagnose subtypes, even when the tissue sample is sparse or unsuitable for conventional molecular testing (1042). Beyond a single cancer type, a pan-cancer classification model has also been developed, which differentiated more than 170 tumor types across all organ sites. Achieving over 97 percent precision across diverse sample types, this approach shows how AI can expand the use of DNA methylation–based tumor classification beyond brain tumors and support diagnosis across a broad range of cancers (1043).

AI applications are also showing promise in predicting when and where in the body cancer will spread and whether it will come back. For example, a recent study showed that ML models predicted aggressive properties of brain tumors from MRI scans of patients, a task that even experienced radiologists have difficulty performing consistently, offering a noninvasive way to identify patients with brain metastases earlier and inform treatment decisions based on likely tumor behavior (1044).

As another example, researchers have recently developed a fully automated AI system that detects and classifies bone metastases on CT scans with high sensitivity and accuracy. The model significantly reduced the time radiologists need to accurately diagnose bone metastases, while improving detection rates, demonstrating its potential to support routine cancer staging and early identification of metastases (1045). Similarly, ML models were able to predict when and where breast cancer was likely to spread, including both local recurrences and distant metastases, thus informing prognosis and helping to guide treatment decisions (1046). These models offer a new approach to risk assessment and enable the selection of patients who may benefit from more intensive systemic treatments.

Advancing New Treatments

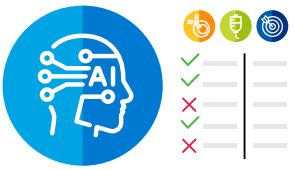
AI is reshaping cancer drug development by streamlining aspects of cancer science and medicine that have traditionally been time-consuming, expensive, and high-risk. By analyzing vast datasets, modeling complex biological systems, and uncovering meaningful insights, AI is helping researchers identify 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 target identification—determining the genes, proteins, or pathways most critical to cancer progression—and drug discovery—finding or designing drugs that can act on those targets (see **Sidebar 27**, p. 90). Innovations such as AlphaFold, which earned the 2024 Nobel Prize in Chemistry for leveraging AI to predict the 3D structure of proteins, are enabling researchers to model the structure of millions of proteins with high accuracy and opening new paths to therapeutic development (1047). At the same time, AI is helping scientists predict and address drug resistance by integrating multi-omic and clinical data to develop more effective, personalized treatment strategies (1048).

AI-driven target identification harnesses large amounts of biological data to determine key vulnerabilities in cancer. A recent study applied AI-powered software to transcriptomic data from adenoid cystic carcinoma (ACC)—a rare type of salivary gland cancer with few treatment options—and identified the protein PRMT5, an enzyme that modifies other proteins to control gene expression, as a promising therapeutic target. They showed that inhibition of PRMT5 suppressed tumor growth in multiple preclinical models and reduced the expression of key drivers of ACC progression, providing a strong rationale for future clinical development of PRMT5 inhibitors as a targeted therapy for ACC patients (1049).

In another study, researchers developed a DL model that integrates multi-omic data and information on known pathways from public databases to predict cancer-driving genes. By modeling interactions between genes, proteins, and RNAs, the tool revealed 57 cancer-driving gene candidates across multiple tumor types, including three genes that had not been identified by other models (1050). These findings highlight the potential of AI to uncover novel, clinically relevant targets, paving the way for the development of more effective and personalized therapies.

AI can also assist with more efficient drug design, predicting drug behavior, and accelerating the identification of effective drug combinations and repurposed therapies. In one study, researchers developed an ML-driven approach to guide combination drug screening by prioritizing which of the 1.4 million possible pairwise combinations of 206 drugs to test in pediatric cancer cell lines. The model accurately predicted previously unknown drug pairings and identified effective combinations confirmed by follow-up experiments after testing only 4 percent of the 1.4 million possible combinations—a task that would have taken a team of trained researchers years to complete (1051). This adaptive screening strategy could help streamline the discovery of promising

In a recent study, **machine learning models evaluated 1.6 million potential anticancer drug combinations against pancreatic cancer to identify 307 promising drug pairs**, including many novel combinations not previously tested experimentally.



Source: (1052).

W82

drug combinations and substantially shorten the timeline for future experimental validation.

AI can also expand treatment options for cancer through drug repurposing—the use of existing drugs approved for non-cancer conditions to treat cancer. Researchers recently developed an ML model that uses patient-specific genomic data, including mutations in non-coding regions of the genome, to identify drugs originally intended for other diseases. By using tumor data from over 5,000 patients, this model identified actionable drugs approved to treat conditions other than cancer for more than 30 percent of cases and successfully validated several predictions in laboratory tests using tumor cells from patients with pancreatic and esophageal cancers (1053).

These findings highlight how AI models can help overcome long-standing barriers in drug discovery by rapidly narrowing down large experimental workflows and guiding the development of more personalized cancer treatments.

Enhancing Clinical Decision-Making

AI-driven technologies are improving clinicians' ability to predict patient outcomes and personalize treatment plans. Digital twins—virtual, continuously updated models of individual patients—are one such technology. Digital twins integrate real-world data from electronic health records (EHRs) and clinical evaluations, alongside multi-omics 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 rare cancers, where they can function as synthetic control arms to augment or replace conventional controls when patient enrollment is limited (1054).

Another emerging application for AI is in cancer surgery. In a recent study, an AI-powered 3D reconstruction system significantly improved lung surgery planning by more accurately identifying critical anatomic features, such as blood vessels and bronchi, thus reducing errors by over 40 percent and preoperative planning time by 25 percent (1055).

At the same time, LLMs are proving valuable for diagnostic and treatment decisions. In a randomized controlled trial, physicians using GPT-4, a large multimodal DL model, outperformed those using conventional resources alone in clinical management tasks, such as considering diagnostic decisions, treatment options, and factors like patient comfort and preferences (1056). Researchers have also recently developed a fully automated clinical AI agent that integrates GPT-4 with precision oncology tools, including models for genomic analysis, histopathology interpretation, image analysis, and web-based search tools. By combining these capabilities, the agent guided clinical decision-making with high accuracy. When tested on 20 realistic, simulated patient cases, this system recommended appropriate treatments and care plans in over 90 percent of cases, nearly tripling the accuracy of GPT-4 alone (1057). Together, these advances are paving the way for smarter clinical support for patients that can deliver more personalized care and shape the future of cancer treatment.

Muscle-invasive bladder cancer (MIBC) 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 DL model that integrates tumor images and gene expression data to predict how patients will respond to chemotherapy. The model accurately identified patients likely to benefit from treatment and revealed key molecular and visual features of tumors associated with treatment response (1058). This approach may help tailor treatment plans for patients with MIBC and reduce unnecessary exposure to toxic therapies.

AI is also being used to predict which patients will respond favorably to immunotherapy. In a recent multicenter study of patients with advanced lung cancer, researchers developed a DL model that analyzes pathology slides to predict who is most likely to benefit from immune checkpoint inhibitors (ICIs). The model's predictions were comparable to current clinical biomarkers, such as PD-L1, and improved when the two approaches were combined, highlighting that this model could help guide treatment decisions and improve patient outcomes (637).

Researchers have also applied techniques from natural language processing (NLP)—a field of AI that includes tools, such as LLMs, that allow computers to understand and use human language—to extract information from EHRs and clinical notes to combine with genomic, demographic, and

treatment data. Using data from nearly 25,000 cancer patients, this approach improved predictions of cancer outcomes, such as survival and risk of metastasis, compared to traditional staging or genomic data alone (1059).

In another study, researchers trained a DL model on data from over 15,000 patients across 38 types of solid tumors to identify indicators of how cancer will progress, and which treatment may be most effective. They uncovered more than 1,300 novel connections between diverse data types—such as body composition, lab tests, and tumor genetics—to uncover mechanisms that help determine how a patient's disease is likely to progress (1060). These findings show the promise of AI in aiding clinicians in prioritizing and optimizing critical patient-specific information and treatment strategies.

Leveraging a novel ML platform that combines drug response data with molecular features from the patient's own cancer cells, researchers have uncovered biomarkers of chemotherapy resistance and identified potential alternative treatments for colorectal cancer patients. The platform accurately predicted clinical outcomes across four diverse cohorts and proposed alternative therapies for treatment-resistant tumors (1061). Another AI tool integrated multi-omic data from lung cancer patients to predict personalized treatment responses, suggest new drug uses, and estimate how well treatments might work and their potential side effects (1062).

AI-guided platforms can also aid in determining how to adjust treatment doses over time. In a recent study, researchers developed an AI tool to guide individualized chemotherapy dosing recommendations based on a patient's treatment response data (1063). The platform enabled real-time dose adjustments and was adaptable to patient-specific changes such as toxicity levels and tumor response, offering a promising path toward safer, more personalized cancer chemotherapeutic regimens.

Fairness and Oversight

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. Researchers have also highlighted the lack of standardized benchmarks in using AI in medicine. Without shared datasets, evaluation methods, or consistent performance metrics, tools may get optimized for narrow clinical contexts—for example, working well only in one hospital's patient population or imaging protocols—without generalizing to broader use (1064). 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 (1065).

While AI holds great promise for improving diagnosis, personalized treatment, and increasing access to care for cancer patients, it may inadvertently worsen disparities. For example, underrepresentation of diverse populations in AI training datasets and unequal access to AI tools, particularly in low-income and rural areas, may exacerbate existing health disparities (1066). Building public confidence in AI will require clear communication, robust data governance, and active engagement with all stakeholders. The future of AI in cancer care will depend on both technological innovation and collective action to ensure these tools are transparent, equitable, and trusted by those that will use them.

CRISPR in Cancer Research and Drug Development

CRISPR-based systems are powerful and versatile gene editing tools that allow researchers to precisely modify DNA. Researchers have harnessed these systems not only to deepen our understanding of mechanisms that drive human diseases but also to explore new ways to treat them. For example, CRISPR can be used to re-create genetic mutations to see how they affect the body, fix or replace faulty genes, add tags to track how genes behave, turn genes on or off without changing the DNA itself, or engineer immune cells to fight disease.

Traditional CRISPR tools are made up of two parts, a programmable RNA guide that can find a specific site in the DNA and a Cas protein that acts like molecular scissors to cut both strands of DNA at that site. After DNA has been cut, the cell's natural DNA repair processes can be harnessed to make changes with high precision and accuracy.

Building on these foundational CRISPR-Cas systems, next-generation CRISPR tools, like base and prime editors, have been developed that allow even more refined edits to be made, down to single letters of the genetic code. Base editors work like pencils that can erase and rewrite a single letter of DNA. These tools work best for changing one nucleotide base to another, for example, switching an adenine (A) to guanine (G) or cytosine (C) to thymine (T) (see **Influences Inside the Cell**, p. 34). Prime editors are more like word processors and can make a wider range of changes, including adding or deleting small pieces of DNA, or swapping multiple letters at once.

These innovative tools are supporting advances in research and clinical development through disease modeling, drug screening, and the development of new therapies. In the context of cancer, CRISPR is being used to uncover how mutations drive tumor development, explore vulnerabilities in cancer cells, and create personalized treatment approaches. The following section describes how gene editing is reshaping our understanding of cancer and accelerating the discovery of innovative, more effective therapies.

Basic Research Discoveries

CRISPR gene editing has rapidly evolved into one of the most transformative tools in basic research. The ability of CRISPR systems to precisely modify genes in living cells has made it possible for researchers to model human diseases and uncover the genetic underpinnings of complex biological processes with unprecedented speed and accuracy.

In a recent study, researchers used base and prime editors to scan tens of thousands of mutations in the *EGFR* gene, a gene frequently mutated in lung cancer, revealing previously unknown variants that drive tumor growth or treatment resistance (1067). This approach not only generated new insights into the genetic drivers of cancer but also demonstrated how precision editing can inform treatment decisions and accelerate the development of personalized therapies.

In another study, researchers used CRISPR to introduce cancer-driving mutations in experimental human brain organoids (see **Sidebar 6**, p. 31), which retain the structural complexity of the developing brain. These organoids provide a powerful platform for studying brain tumor development and can be used to investigate the specific roles of individual gene variants (1068). Advances in basic research using CRISPR technologies will continue to enable the development of more biologically relevant experimental models and deepen insights into cancer biology.

Drug Development

By enabling researchers to systematically investigate the molecular pathways that drive cancer growth, resistance, and immune evasion, CRISPR is contributing to advances in drug development strategies. With its unparalleled precision and adaptability to large experimental designs, CRISPR allows researchers to perform genome-wide functional screens that can accelerate the development of precision cancer therapies in ways not previously possible.

Recently, CRISPR screening has been used to identify novel immune-related targets that boost the effectiveness of chimeric antigen receptor (CAR) T-cell therapy and reveal mechanisms of immune evasion that tumors use to resist treatment, advancing the search for more effective immunotherapies (1069).

Researchers have also developed a CRISPR screening platform to identify synthetic lethal interactions, which occur when two otherwise tolerated gene changes occur simultaneously and lead to cell death, across multiple cancer types. By pairing these results with large-scale drug sensitivity data from tumor cell line screens, they identified gene alterations that sensitize cancer cells to specific drugs, offering a systematic approach to match cancer patients with targeted therapies and advancing synthetic lethality-based treatment strategies (1070).

These findings demonstrate how CRISPR technologies can be used to bridge basic discovery and actionable clinical insight to accelerate cancer drug development.

Next-Generation Treatments

Recent innovations in CRISPR-based technologies are rapidly advancing toward the clinic, offering tools to correct genetic defects, reprogram immune cells, and remodel the TME (see **Tumor Microenvironment**, p. 45) directly in patients. Across solid tumors and blood cancers, these technologies are being explored not only to enhance existing therapeutic strategies, such as immunotherapies and adoptive cell therapies, but also as a treatment itself.

In several recent studies, CRISPR-based systems have been used to improve the effectiveness of established treatments by activating the immune system. For example, researchers have enhanced the efficacy of adoptive T-cell therapies (see **Sidebar 41**, p. 135) by increasing how long T cells can be active and how quickly they remove cancer cells in both blood cancer and solid tumors (1071). In addition, researchers have genetically engineered natural killer (NK) cells to resist immunosuppressive signals in the TME and improve clinical performance of immunotherapy (1072). Tumor-infiltrating lymphocytes (TILs) modified with CRISPR to block proteins that weaken the immune system are also showing early promise in clinical trials (1073). These advances contribute to a growing trend of using CRISPR to reprogram immune cells for greater antitumor potency (1074–1076).

Researchers are also exploring the potential of CRISPR itself as an anticancer treatment. Base and prime editors provide a way to precisely rewrite faulty DNA without cutting it, offering the potential to fix cancer-causing mutations with remarkable accuracy (1077). RNA-targeting CRISPR strategies are also being used to turn off genes that help cancer evade the immune system without changing DNA, opening the door to more tailored immune-based treatments.

At the same time, researchers are also developing advanced delivery systems that send CRISPR directly to tumors. For example, researchers have recently developed nanoparticles that cross the blood–brain barrier, a protective layer of tightly packed cells that protects the brain from harmful substances, and activate gene editing only within glioblastoma tumor cells (1078). In another study, an EGFR-targeted nanoparticle was developed that delivers CRISPR to head and neck cancers, resulting in complete disappearance of tumors in some animal models (1079).

Although these innovations are highly promising, it is important to note that most CRISPR-based therapies are still in early stages of development. These technologies must undergo

rigorous testing in clinical trials to determine their safety, efficacy, and long-term effects in the human body. Continued research is essential to ensure that these powerful tools can be safely and effectively integrated into cancer treatment.

Liquid Biopsy in Cancer Care

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 includes circulating tumor cells (CTCs), cell-free DNA (cfDNA) such as circulating tumor DNA (ctDNA), and exosomes—tiny, membrane-bound vesicles that transport proteins, RNA, and other molecules between cells. These materials can be analyzed to uncover molecular alterations associated with cancer.

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. As such, liquid biopsy approaches can enhance early detection (see **Advances in Minimally Invasive Screening Approaches**, p. 84), diagnosis, treatment selection, and monitoring of disease progression and recurrence (see **Sidebar 55**, p. 204). The following section highlights recent research exploring how liquid biopsies are being leveraged across the cancer continuum.

Diagnosing Cancer and Predicting Metastases

Emerging research in liquid biopsy is revealing powerful new strategies for detecting cancer earlier and diagnosing the disease more accurately than ever before. Liquid biopsies at diagnosis have been studied for both liquid and solid tumors. As an example, researchers have developed a sequencing method that detects ctDNA with high precision and accuracy from a small blood sample in children newly diagnosed with leukemia, offering a noninvasive alternative to bone marrow biopsy while capturing a broad spectrum of tumor-specific alterations (1080).

Liquid biopsies can also identify patients at the highest risk for cancer spread. In individuals with pancreatic cancer, detection of mutant KRAS ctDNA was strongly associated with metastatic tumors that were difficult to detect by conventional methods and poor survival outcomes, offering new insights into disease biology and aiding decisions about surgery and treatment intensity (1081). Together, these studies underscore the growing impact of liquid biopsy and ctDNA analysis in expanding the reach of cancer diagnosis and improving risk stratification for metastatic progression.

Monitoring Treatment Response and Predicting Resistance

Liquid biopsy can also be used to monitor how tumors respond to treatment and to detect the emergence of resistance. Mutations in the *KRAS* gene are common in colorectal and pancreatic cancers, with G12C being a clinically important subtype now targetable by approved therapies. In a recent study, ctDNA profiling was used to assess how tumors with KRAS G12C mutations respond to treatment. Researchers found that nearly half of the patients had additional mutations that may interfere with the effectiveness of KRAS G12C inhibitors (1082). These findings underscore the importance of pre-treatment molecular profiling to identify changes in the tumor that might reduce treatment effectiveness.

Monitoring dynamic ctDNA changes during treatment can signal emerging resistance or treatment success. In non–small cell lung cancer, early disappearance of detectable KRAS G12C ctDNA following treatment with sotorasib—a targeted therapy that blocks the KRAS G12C protein—was linked to better outcomes, while persistent ctDNA predicted poor response (88). In another study, a greater than two-fold drop in ctDNA after one chemotherapy cycle was indicative of sensitivity to platinum-based treatment in small cell lung cancer and was associated with longer survival (1083).

Early changes in ctDNA levels after starting treatment have also been used to predict treatment outcome and monitor immune response. In a phase II clinical trial, early changes in tumor-agnostic ctDNA features within the first week of starting treatment with the ICI pembrolizumab predicted both progression-free survival and overall survival across solid tumors (1084).

Together, these findings position ctDNA as a critical tool for predicting resistance and assessing treatment effectiveness, with ongoing research also exploring its use in pediatric cancers (1085).

Detecting Minimal Residual Disease and Recurrence

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

SIDEBAR 55

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.

Promise of Liquid Biopsy

- **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.
- **Reduce potential physical harms** associated with a medical procedure, because these tests are minimally invasive.
- **Minimize the anxiety** associated with laboratory tests, especially among children and older adults.

Potential Drawbacks

- **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.

Liquid biopsy provides a powerful tool to guide precision medicine, helping doctors monitor cancer in real time and adapt treatments based on a patient's tumor evolution.

or absence of ctDNA following surgery or systemic therapy can serve as a powerful indicator of patient outcomes and guide posttreatment decisions.

In colorectal cancer, a recent study showed that patients with detectable ctDNA after surgical removal of the tumor had worse survival outcomes, while sustained ctDNA clearance

during additional chemotherapy predicted long-term benefit (1086). Clinical trials have also shown that ctDNA measurement as a marker of MRD can guide treatment decisions in early-stage disease. In colorectal cancer, researchers found that using ctDNA to inform adjuvant chemotherapy decisions significantly reduced unnecessary treatment without compromising long-term survival (1087).

Similarly, in metastatic kidney cancer, researchers showed that tracking ctDNA over time can offer important insights for patients receiving standard immunotherapy or targeted drugs. They found that patients whose ctDNA remained undetectable had much longer periods without disease progression, while those with detectable ctDNA were more likely to experience relapse, revealing its potential to monitor remission and relapse in real time (1088).

In another study in melanoma, ctDNA detected after surgery identified patients at highest risk of recurrence, and its continued presence during follow-up treatment signaled early relapse and poor survival despite standard therapy (1089). In cervical cancer, results from a phase III clinical trial showed that detection of ctDNA after treatment predicted relapse and survival. Personalized ctDNA tests could detect signs of cancer recurrence months before it appeared on scans, while patients with detectable ctDNA after treatment were significantly more likely to experience relapse (1090). These studies demonstrate how liquid biopsy approaches are helping clinicians personalize posttreatment care, offering a less invasive, highly sensitive tool to detect recurrence and plan clinical care.

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 55**, p. 204). Researchers have highlighted key barriers to ctDNA adoption, some of which include a variable amount of detectable material and lack of standardized protocols (1091). 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. Among the most promising advances are next-generation cellular immunotherapies and molecularly targeted therapies, which are expanding therapeutic possibilities for patients with aggressive or treatment-resistant cancers (see **Sidebar 37**, p. 110).

For example, in a recent study, researchers engineered allogeneic CAR T cells—immune cells derived from healthy donors rather than the patient—to express an HIV (human immunodeficiency virus) protein called Nef, which has the natural ability to protect the engineered cells from the patient's immune system, thus improving their survival (1092). This strategy could pave the way for more accessible, durable, and potent T-cell therapies for a broader population of patients. Researchers are also exploring strategies for CAR T-cell therapies targeting the most intractable solid tumors, such as glioblastoma. Recent trials have shown encouraging results using CAR T cells in brain tumors targeting multiple tumor-specific proteins, novel surface proteins, and combinatorial approaches (649,1093).

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. 31). 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, and 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 56**, p. 206). 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. Building on these successes, researchers are now exploring the development of preventive vaccines against cancers that target genetic mutations or molecular characteristics of cancer itself (see **Genetic Insights Advancing Cancer Risk Reduction and Interception**, p. 85).

For example, an ongoing trial is using a KRAS-targeted peptide vaccine in individuals with KRAS mutations who are at higher risk of developing pancreatic cancer (1094). Peptides—short chains of amino acids that join together to form proteins—are often used in vaccines to stimulate specific immune responses. Preventive cancer vaccines offer an advantage in the likelihood of a strong, lasting response over therapeutic vaccines (1095). As research in this field continues to advance, these vaccines hold great potential to reduce cancer risk, ease the burden of continuous monitoring, and reshape how we approach cancer prevention.

Therapeutic cancer vaccines activate a patient's immune system to recognize and destroy cancer after it has developed, often by

SIDEBAR 56

Next-generation KRAS Therapies

KRAS 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 block other common KRAS mutations, such as G12D, G12V, and G13D.

RAS(ON) TRI-COMPLEX INHIBITORS: These inhibitors block KRAS when it is in its active, GTP-bound "on" state by forming a three-part complex that stops it from signaling.

SYNTHETIC GAP ACTIVATORS: These drugs aim to reactivate the normal "off switch" in mutant KRAS proteins, helping to shut down their cancer-promoting activity.

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

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.

DENDRITIC CELL (DC) VACCINES: These vaccines can teach immune cells to recognize and attack KRAS-mutant cancer cells.

MULTI-EPITOPE PEPTIDE VACCINES: These vaccines target several KRAS mutations at once to create a broader and more powerful immune response.

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.

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 drugs reach cancer cells more easily and support immune cell entry.

targeting unique markers found on cancer cells. These vaccines can complement existing therapies and may be especially effective when used in combination with ICIs, chemotherapy, or molecularly targeted therapies (1096,1097). 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 uses an RNA-based approach that can be tailored to encode multiple tumor-specific neoantigens—mutated proteins that are unique to cancer cells. In a recent clinical trial in patients with pancreatic cancer, an individualized RNA vaccine, given alongside the ICI atezolizumab and chemotherapy, triggered vaccine-specific T-cell responses in half of the patients, resulting in delayed cancer recurrence and favorable survival outcomes (1098).

Dendritic cell (DC)-based vaccines represent another strategy for cancer treatment. In a pilot study of patients with early-stage HER2-positive breast cancer, injection of a DC vaccine targeting HER2 was found to be safe and immunologically active, driving increased T-cell infiltration in tumors and potentially enhancing complete response rates when given before chemotherapy (1099). In another trial, a DC vaccine with personalized mutant KRAS peptides is being tested in patients with pancreatic cancer, demonstrating feasibility and laying the foundation for further study of DC vaccines in one of the deadliest cancer types (1100).

Neoantigen-targeting peptide vaccines are another promising therapeutic cancer vaccine strategy. A personalized neoantigen vaccine trial in patients with kidney cancer who were considered at high risk of recurrence after having their tumors completely removed through surgery demonstrated strong immune system activation, targeting key driver mutations and inducing durable T-cell responses, with all nine vaccinated patients remaining disease-free after a follow-up of more than 3 years (1101). In another trial, a shared antigen vaccine, which targets mutations or proteins commonly found across patients' tumors, is being tested in patients with resected pancreatic and colorectal cancer. This vaccine targets mutant KRAS peptides and is being evaluated in combination with nivolumab and ipilimumab, investigating potential combined effects between vaccine-induced immune response and ICIs (1102).

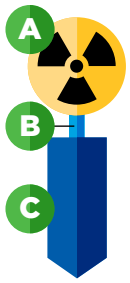
Researchers have also recently shown promising results from a trial that used personalized vaccines targeting neoantigen peptides predicted in individuals with high-risk solid tumors and hematologic malignancies. All trial participants showed positive neoantigen-specific T-cell and B-cell immune responses. The study also revealed that even tumors with relatively few genetic mutations could be effectively targeted using tailored neoantigen selection, and that vaccine-induced immune responses correlated with long-term survival in some patients (1103).

SIDEBAR 57

Radioligand Therapy

Radioligand therapy (RLT) is an innovative cancer treatment that delivers radiation precisely to cancer cells using a ligand—a molecule that attaches to specific proteins on the surface of cancer cells—allowing for targeted treatment with minimal damage to healthy tissue. RLT pairs the precision of molecular targeting with the potent, localized power of radiotherapy to treat cancer effectively.

Key Components of RLT



A RADIOISOTOPES

Common types include α-emitters (e.g., actinium-225) that deliver high-energy radiation over a short range and β-emitters (e.g., lutetium-177) that penetrate further into tissue.

B LINKERS

Chemically connect the ligand to the radioisotope and influence stability and release.

C LIGANDS

Bind selectively to cancer-specific markers.

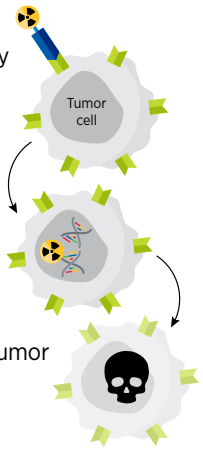
How Radioligand Therapy Works

A **ligand** (small molecule or peptide) targets a protein uniquely expressed on cancer cells.

A **radioactive isotope** is attached to the ligand.

The compound is injected and circulates through the body, binding selectively to tumor cells.

Once bound, it is internalized by tumor cells, where it delivers radiation that kills the cancer cells while minimizing harm to healthy tissue.



Radiopharmaceutical Therapy

Radiopharmaceutical therapies, including radioligand therapies (RLTs), are a rapidly evolving class of cancer therapeutics that use radioactive compounds to deliver cytotoxic radiation directly to cancer cells. RLTs combine a

radioactive compound with a targeting agent that binds to specific proteins found on cancer cells. Once bound, high-energy radiation is delivered directly to the cancer cells while avoiding surrounding healthy cells, offering a highly localized, tumor-specific approach to treatment (see **Sidebar 57**, p. 207). As of June 30, 2025, FDA has approved two RLTs—lutetium-177 dotatate (Lutathera) for neuroendocrine tumors in 2018 and lutetium-177 vipivotide tetraxetan (Pluvicto) for metastatic prostate cancer in 2022 (see **Applying Precision to Radiation Therapy**, p. 105).

The effectiveness of these therapies has brought about a wave of innovation and clinical exploration. The success of Pluvicto in targeting prostate-specific membrane antigen (PSMA)–expressing prostate tumors has led to a four-fold increase in radiopharmaceutical use in metastatic prostate cancer since 2021, and radiopharmaceuticals now represent the second most common treatment for these patients after chemotherapy (497). The field is also advancing rapidly in breast cancer, for which clinical trials are exploring investigational RLTs in combination with bispecific antibodies and immunotherapies to overcome tumor heterogeneity and enhance immune activation (562).

Emerging technologies are further expanding the potential of radiopharmaceuticals by refining delivery methods and exploring novel isotopes. In a first-in-human trial for glioblastoma, instead of using a radioactive isotope bound to a ligand, researchers used a pressure-driven technique to deliver a novel beta-emitting isotope, rhenium-186, encapsulated into nanoliposomes—tiny, hollow spheres made from natural substances like those found in cell membranes—directly into brain tumors. This method bypasses the blood–brain barrier and enables high local radiation doses, exceeding those achievable with external beam radiation therapy, with minimal systemic toxicity. Patients who received more than 100 Gy (units of ionizing radiation dose) experienced a median survival of 17 months—compared to 8 months with standard of care treatment—highlighting the importance of precise, localized delivery in treating difficult-to-access tumors (1104).

In the past decade, more than 160 clinical trials have been launched globally to evaluate RLTs across a range of tumor types (497). With ongoing advances in research, radiopharmaceuticals hold promise as the next generation of precision therapies for patients with cancer.

Advancing Cancer Science and Medical Research Through Evidence-based Policies

IN THIS SECTION, YOU WILL LEARN:

- Robust investment in federal agencies, including NCI, is essential to advancing cancer screening, treatment, and survivorship.
- Support for education and training programs is vital to developing a medical and scientific workforce that will lead the next generation of cancer research and care.
- FDA plays a pivotal role in accelerating access to safe and effective cancer therapies by encouraging innovative clinical trials that promote broad participation of patients across the United States.
- Federal agencies, including NIH, FDA, CDC, and VA, are implementing evidence-based policies and programs to reduce the risk of cancer and lessen the disparities in cancer care that currently exist in certain populations.

The remarkable progress against cancer has been driven by sustained federal investments in biomedical research. Key agencies, including the National Institutes of Health (NIH), National Cancer Institute (NCI), US Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC) play vital roles in cancer prevention, early detection, treatment, and survivorship. For decades, these agencies have served as a catalyst for advancing cancer science and improving patient care.

Strategic investments in research have led to groundbreaking discoveries and more targeted treatments (see **Basic Research Decoding Cancer's Complexities**, p. 31), while efforts to strengthen the cancer workforce, modernize regulatory science, and expand access to prevention and screening have accelerated progress across the cancer continuum. As cancer research and care become increasingly complex, sustained funding for federal agencies and aligning public policy with the latest scientific evidence will remain essential to improving outcomes for all patients with cancer and ensuring a healthier future for them.

Investing in Research to Achieve a Healthier Future

Decades of investment and support by the United States (US) government have been critical to the development of new cancer treatments and the decline in the cancer mortality rate. Among the Department of Health and Human Services (HHS) agencies responsible for supporting this progress is NIH, the world's largest public funder of biomedical research (1105). Of the 27 institutes and centers (ICs) at NIH, NCI advances cancer research by providing individual grant funding for accomplished scientists and supporting broader clinical trials, while also training the next generation of researchers (1106).

An additional component of NIH that is separate from the 27 ICs is the Advanced Research Projects Agency for Health (ARPA-H), which funds high-potential, high-impact biomedical research projects that cannot be realized through traditional commercial or research means (1107). Since the creation of ARPA-H in March 2022, the agency has launched

multiple projects intended to improve cancer treatment, detection, and patient outcomes (1108).

FDA is another HHS agency that plays a major role in supporting efforts to prevent and treat cancer. Among FDA centers contributing to this mission are the Oncology Center of Excellence (OCE), which convenes experts to conduct expedited reviews of oncologic medical products (1109); and the Center for Tobacco Products (CTP) (1110), which regulates the sale of tobacco products and educates the public about the dangers of tobacco use.

As the primary public health agency in the United States, CDC is crucial to cancer prevention efforts. Through its Division of Cancer Prevention and Control (DCPC), CDC provides funding and support for the National Program of Cancer Registries, the largest disease surveillance system in the United States, which aims to collect, analyze, and disseminate data on cancer incidence to inform prevention and control efforts. Additional DCPC programs include the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) and the Colorectal Cancer Control Program (CRCCP), which encourage cancer screenings and support various cancer prevention initiatives (1111,1112).

Thanks to the investments and support provided by these federal agencies, the United States has seen tremendous progress against cancer, most prominently a drop in the cancer mortality rate. Since reaching its highest point in 1991, the overall age-adjusted cancer death rate has declined by 34 percent (6). This decrease would not have been achievable without the advancement of lifesaving cancer therapies. For instance, NIH funding played a central role in the development of 354 out of 356 drugs approved by FDA between 2010 and 2019, including 126 first-in-class products to treat cancer and other diseases (70).

Although cancer-related health outcomes have improved significantly, cancer remains the second-leading cause of death in the United States, and the need for additional investment in cancer research persists. An estimated two million new cancer diagnoses are projected in the United States in 2025, with a total of 618,000 people expected to die from the disease (6). Additionally, between 2010 and 2019, incidence rates of 14 cancer types increased among people under the age of 50 (see **The Growing Population Burden of Cancer**, p. 23). Among these, cancers of the female breast, colon and rectum, kidney, and uterus contributed to the majority of the additional early-onset cancer diagnoses in 2019 (44).

At the same time, improvements in early detection and treatment have led to a growing population of cancer survivors who require continued care and innovation. There were an estimated 18.6 million cancer survivors in the United States in 2025, and this number is projected to exceed 22 million by 2035 (9). This underscores the growing importance of sustained investment in medical research.

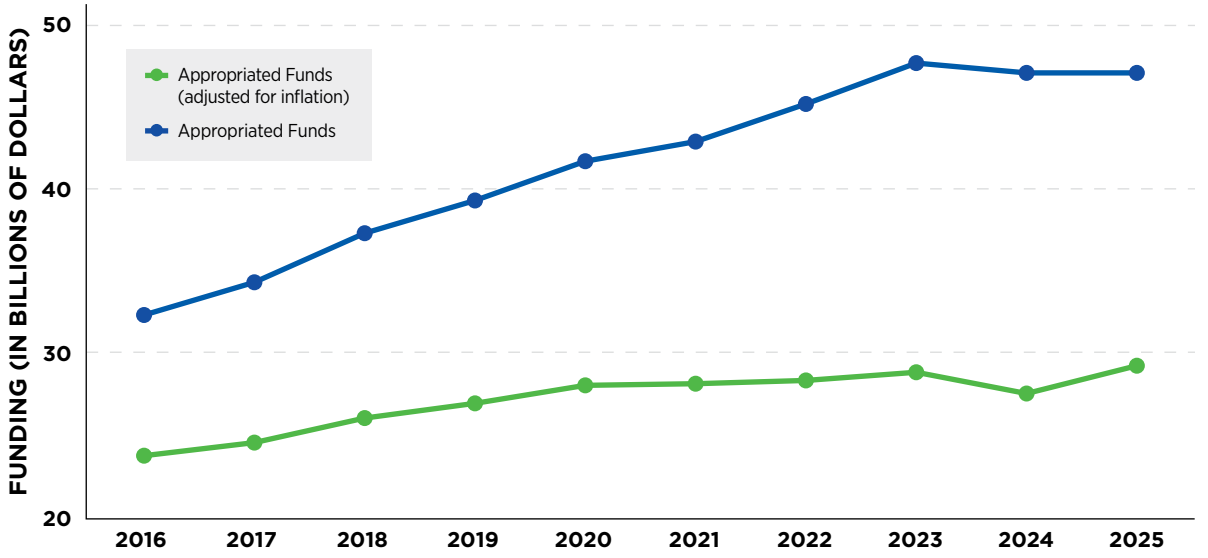
Federal funding is crucial for training the next generation of cancer researchers, ensuring a robust scientific workforce capable of tackling complex challenges and driving advancements in cancer prevention, detection, and treatment. NIH provides vital funding for training programs, fellowships, and career development opportunities that are instrumental for early-career researchers. Funding cuts will impact the training pathway of graduate students, postdoctoral fellows, and early-career researchers, slowing down the development of new cancer therapies and imperiling progress. This includes a decline in physicians pursuing additional research training to become physician-scientists, many of whom have contributed to pivotal discoveries of novel therapies (1113). Federally funded training awards and programs are a vital component of training and retention for the next generation of independent cancer researchers (1114). In addition, these training programs are uniquely positioned to improve equity in cancer outcomes and have a track record of helping diversify the biomedical research workforce and reduce cancer health disparities (1115). Disruptions to NIH-funded training programs have already reduced the number of students pursuing careers in cancer research, limited opportunities for early-career scientists, and stymied the development of a knowledgeable workforce (1116–1118).

NIH has traditionally received strong bipartisan support from Congress and the White House. After more than a dozen years of stagnant funding, NIH received a budget increase every year between fiscal year (FY) 2016 and FY 2023 totaling $17.6 billion—a 57 percent increase from FY 2015. However, FY 2024 marked the first occasion in roughly a decade that Congress did not provide NIH with a funding increase, largely due to caps on discretionary non-defense spending imposed by the Fiscal Responsibility Act (1119). For FY 2025, Congress kept NIH funding consistent with the FY 2024 level at approximately $47 billion. Importantly, the costs of biomedical research have been steadily increasing due to several factors, including increasing inflation, rising clinical trial complexity, and growing staffing needs (1120,1121). Without federal funding increases to keep pace with both rising research costs and inflation, these escalating expenses will limit innovation, slow progress, and delay treatments for the patients with cancer, such as **Richard Schlueter** (see p. 212), who desperately need them.

Support for medical research also provides substantial economic benefits to the US economy. NIH funding for extramural research supports the purchase of goods, services, and materials, which contributes to job creation and economic growth in communities across the nation. In FY 2024, NIH awarded $36.94 billion to researchers across all 50 states and Washington, DC, supporting 407,782 jobs and generating $94.58 billion in economic activity (see **Sidebar 5**, p. 27) (78). Strong NIH

FIGURE 25

NIH Funding and the Importance of Continuing Robust Increases



Despite growing $15 billion over the past 10 years (blue line), the National Institutes of Health (NIH) base budget has barely increased when accounting for inflation as determined by the NIH Biomedical Research and Development Price Index (green line). Largely stagnant funding in fiscal year (FY) 2024 and FY 2025, along with steep cuts proposed in the president's FY 2026 budget request, further jeopardizes NIH's capacity to fund research and training.

funding also helps maintain the United States' position as a global leader in medical research. As the United States' peer nations continue to invest more of their gross domestic product into medical research, the need to continue to increase funding for NIH will become increasingly more important (1122).

Funding for NIH stagnated in the early 2010s. When adjusted for inflation, years of flat funding represented a decline in NIH's ability to fund research and training. However, between FY 2016 and FY 2023, Congress provided NIH with robust annual budget increases, resulting in a 57 percent increase ($17.6 billion) during that time span. Unfortunately, the momentum stopped in FY 2024 and FY 2025 when NIH's budget was held flat, potentially slowing progress in many areas of cancer research (see **Figure 25**, p. 211).

In May 2025, the White House released the president's budget request for FY 2026. It recommended $27 billion in funding for NIH, a proposed 40 percent decrease from its current allocation. If enacted, this drop in funding would severely impact NIH's ability to support biomedical research and its lifesaving impact on all Americans. The FY 2026 budget request reflects just a small part of the Trump Administration's proposals and policies that have impacted federal investment in research. In February 2025, the administration proposed a 15 percent cap on reimbursement of indirect costs for all NIH grants (1123). Indirect costs refer to essential institutional expenses that support research, but are not tied to a specific project, such as facility maintenance, utilities, administrative support, and compliance with federal regulations. These costs are vital to keeping research programs operational. According to the United for Medical Research (UMR) *2024 Annual Economic Report*, indirect costs account for approximately 24 percent of the total economic activity generated by NIH funding (78). Under the direction of the administration, NIH has also significantly delayed new notices of grant awards and canceled more than 715 grants worth $815 million. Other directives include a reduction in workforce affecting more than 1,300 NIH personnel and the cancellation of numerous contracts (1124).

While the president's annual budget request is the first step in the appropriations process, ultimately, it is the responsibility of Congress to draft, negotiate, and enact spending bills that will determine the FY 2026 budget for NIH. During initial

continued on page 214

Disrupted Funding, Delayed Treatment: The Consequence of the NIH Funding Crisis

Richard Schlueter
AGE: 56 | BROOKHAVEN, GEORGIA

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In February 2024, Richard Schlueter, an attorney from Brookhaven, Georgia, received a diagnosis that would change his life: head and neck squamous cell carcinoma. A devoted husband, father of three, and managing partner at a consumer litigation firm, Richard had always prioritized his health. He exercised regularly, maintained a healthy lifestyle, and never missed his annual physical. When Richard noticed a metallic taste in his mouth and saw white pustules on his tonsil, he knew something wasn't right.

"I remember standing in the bathroom late at night, using a toothbrush to push back my tonsil and seeing those spots," Richard recalled. "I have a science background, and I knew immediately this wasn't normal."

The diagnosis came just days before Valentine's Day. Richard and his wife Michelle were stunned. "We just went upstairs, hugged each other, and cried," Michelle said. "It was gut-wrenching."

Richard began treatment at Emory University with a curative plan of 7 weeks of chemotherapy and proton therapy. The prognosis was optimistic, doctors gave him a 90 to 95 percent chance of cure. However, by July a follow-up scan revealed that the cancer had spread to his lungs and chest cavity. The Schlueters' world shifted from curative intent to palliative care. "It was devastating," Richard said. "I'm a fact finder by nature, and I was determined to find a path forward."

Their search led them across the country from the University of Texas MD Anderson Cancer Center in Houston to the Dana-Farber Cancer Institute in Boston, and eventually to the National Institutes of Health (NIH), where Richard qualified for a leading-edge clinical trial involving tumor-infiltrating lymphocytes (TILs), a personalized immunotherapy designed to harness and amplify his own immune cells to fight the cancer. The Schlueters found hope again. "Patients often call NIH the National Institutes of Hope," Michelle said. "That's exactly what it felt like."

Richard underwent surgery at NIH to gather tumor tissue from his lungs. These tumor samples were examined in a lab where they isolated the T cells that had infiltrated the tumor, and these T cells, called TILs, were multiplied and then frozen until the time for infusion. But just as the therapy was nearing readiness, NIH announced delays due to staff cuts. Essential lab personnel had been terminated, extending the final preparation timeline from 3 weeks to up to 10 weeks. For Richard, whose cancer was progressing rapidly, this delay was not just inconvenient, it was life-threatening.

"My therapy was in a freezer, ready to go," he said. "But I was told I might not get it in time. I'm petrified." Richard added that his cancer was spreading; he knew the trial was his best chance.

The delay was more than a bureaucratic hiccup—it was a deeply personal blow. In May 2025, Richard was still golfing with his son and nephew. By June, he was struggling to walk down the aisle to renew his vows with Michelle on their 30th wedding anniversary. "He's always been strong," Michelle said. "But now, even getting out of a chair is hard."

Despite the physical toll, Richard remains focused on the bigger picture. "Even if this therapy doesn't save me, I hope my experience helps others," he said. "I feel like a test pilot. If it works, it could change lives."

The Schlueters' experience is a stark illustration of how disruptions in federal biomedical research infrastructure can have devastating consequences for patients. "We're not just statistics," Michelle emphasized. "Behind every trial, every therapy, is a family fighting for more time."

After months of uncertainty, Richard was finally called back to NIH in late July 2025. On July 24, he began lymphodepletion, and on August 1 he finally received his TIL infusion. While this brought relief, the Schlueters emphasized that no patient should have to fight for access to a treatment already prepared. They immediately began contacting their congressional representatives to highlight the impact of budget cuts. "We are angry and upset," Michelle said, "and we spoke out not just for Richard, but for every family facing these delays."

Their message to Congress is clear: Fund cancer research robustly and consistently. Avoiding interruptions in clinical trials and staffing is not just a matter of scientific progress; it's a matter of life and death. "We need to protect the integrity of institutions like NIH," Richard said. "Because when science is disrupted, hope is delayed—and for patients like me, time is everything."

"When science is disrupted, hope is delayed—and for patients like me, time is everything."

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

congressional hearings on the president's FY 2026 budget request, lawmakers from both parties have criticized the administration's proposed cuts to NIH's budget, as well as the administration's proposal to cap the reimbursement of indirect costs. However, many Republican lawmakers are also focused on advancing the president's agenda to reduce federal spending. And with Republican control of both the Senate and the House of Representatives, the future of investment in medical research remains uncertain. Thus, it is imperative for the medical research community to remain actively engaged with Congress, requesting that they prioritize NIH funding and support the development of lifesaving treatments and therapies.

A Diverse Cancer Research and Care Workforce Drives Innovation

While the administration's position has been to eliminate programs and grants related to diversity, equity, and inclusion, the American Association for Cancer Research (AACR) strongly believes that to continue building on the monumental progress that has been made in cancer research and patient care during the past few decades, a diverse workforce is essential.

Recommendations for Training the Next Generation of Cancer Researchers

- **Build and sustain partnerships** across training programs and workforce entities.
- **Increase access to training** and career development opportunities.
- **Improve early education** efforts and the training pipeline.
- **Require the tracking of trainees** and evaluation of training programs.
- **Strengthen the mentoring infrastructure** and grow a network of mentors and mentor advocates.
- **Provide training in focused areas** to address current gaps and anticipate future needs.
- **Deliver consistent** professional and wellness **support**.

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A diverse scientific workforce is more likely to ask different questions, develop varied study designs, and adopt many different approaches to data collection and interpretation, ultimately expanding the scope of scientific knowledge. Research and health care are strengthened when individuals with unique perspectives and educational backgrounds work together (12,1125).

Applying Regulatory Science to Ensure Safe and Effective Cancer Therapies

FDA plays a central role in safeguarding public health by approving medical products, including cancer therapies, that are safe and effective. The agency provides comprehensive oversight across every stage of the drug development process, including from early-stage laboratory research through clinical trials and long-term post-approval monitoring.

Over the past few decades, the cancer research landscape has significantly evolved, marked by increasing global collaboration and growing complexity in scientific methods, data integration, and regulatory challenges. In response, FDA has modernized its approach to keep pace with rapid scientific advancements. A major milestone in this evolution was the establishment of OCE in 2017, which was included as part of the 21st Century Cures Act (see **Sidebar 58**, p. 215). This cross-center initiative brings together expertise from the

Project Optimus: A New Era in Oncology Dosing

Project Optimus, led by OCE, **is reshaping how cancer therapies are dosed.** Rather than relying on the maximum tolerated dose—a traditional approach commonly used in chemotherapy—this initiative calls for earlier, more rigorous evaluation of dosing to prioritize patient safety, tolerability, and long-term outcomes. By shifting expectations for dose-finding studies, Project Optimus is driving more thoughtful, evidence-based trial designs and helping to ensure that patients receive treatments that are not only effective, but also better tolerated.

Source: (1127).

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SIDEBAR 58

FDA Milestones in Cancer Drug Development (2011–2025): 15 Years of Progress in Advancing Oncology Innovation

Looking back over the last 15 years, the US Food and Drug Administration (FDA) has transformed how cancer therapies are developed, reviewed, and approved. From the creation of expedited approval pathways to the launch of the FDA Oncology Center of Excellence (OCE) in 2017, FDA has responded to the growing complexity of cancer research with bold regulatory innovation. This timeline highlights key milestones that have helped accelerate access to safe, effective cancer treatments—bringing new hope to patients across the globe (1128).

2012 The FDA Safety and Innovation Act is signed into law, creating Breakthrough Therapy Designation—a major milestone for speeding up the development of transformative drugs, especially in oncology.

The Patient-Focused Drug Development initiative is launched to better integrate patient voices into regulatory decision-making, including those with cancer.

2016 The 21st Century Cures Act is passed, modernizing clinical trials and laying the groundwork for more integrated cancer therapy reviews.

2017 OCE is established under the 21st Century Cures Act.

OCE begins unifying regulatory efforts across CDER, CBER, and CDRH for a more integrated review of oncology therapies.

Approval of OCE's first anticancer therapy: Bavencio (avelumab) indicated for Merkel cell carcinoma.

2018 Debut of the Real-Time Oncology Review program to enable faster, more efficient regulatory decisions for cancer therapies.

2019 OCE launches Project Facilitate, a pilot program supporting expanded access to investigational oncology therapies for patients with unmet needs.

2020 In response to COVID-19, FDA adapts oncology trial oversight with virtual inspections, flexible trial designs, and digital health tools—many of which persist post-pandemic.

2021 FDA announces Project Optimus, a major initiative to reform dose optimization practices in oncology drug development.

2022 FDA strengthens post-marketing commitments and accelerated approval oversight, ensuring confirmatory trials are completed promptly, particularly in cancer.

FDA releases the first guidance on Diversity Action Plans.

2023 Launch of Project FrontRunner, aimed at expanding use of accelerated approval in earlier lines of cancer therapy (e.g., neoadjuvant settings).

2024 Greater emphasis on integrating real-world evidence and patient-reported outcomes in cancer drug evaluations.

2025 OCE celebrates eight years of operation and continues to modernize oncology regulatory science through data innovation, AI-assisted trial designs, and international collaboration.

CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health.

Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) to streamline the review and approval of anticancer therapies and devices. Since its launch in 2017, OCE has supported over 400 approvals for anticancer therapies, significantly surpassing the 239 approvals in the nine years prior (2008–2016) (1126).

This progress has been made possible through sustained funding from Congress and user fees authorized by the federal law, which support the infrastructure needed to adapt regulatory science to new frontiers in precision medicine, immunotherapy, and patient-focused care. As the cancer research landscape continues to evolve, FDA remains committed to modernizing the drug development process, expanding access to innovation, and accelerating the delivery of safe and effective treatments to those who need them most.

Increasing Access to and Decentralizing Trials

Clinical trials have been a cornerstone of progress against cancer, ushering in breakthrough therapies and deepening our understanding of cancer biology (see **Innovations in Cancer Clinical Trials**, p. 90). However, access to these trials has historically been limited. Most were conducted at large academic medical centers and primarily accessible to patients with the resources, proximity, and health status required for enrollment. Over the past 15 years, cancer clinical trials have undergone a significant transformation—from rigid, centralized models to more inclusive, patient-centered approaches. This evolution has been driven by the urgent need to expand access, improve participation, and ensure that the benefits of scientific discovery are equitably distributed across all populations affected by cancer.

The COVID-19 pandemic marked an inflection point, accelerating the adoption of innovations designed to make clinical trials more accessible. The rapid integration of remote and virtual care paved the way for decentralized clinical trials, a model that allows participants to engage from home through digital tools such as wearable devices, mobile health apps, and telemedicine platforms. These technologies have proven to be effective mechanisms to reduce access barriers and enhance participant diversity.

FDA has played a pivotal role in advancing equity in clinical research. Over the past decade, the agency has developed cancer-specific guidance aimed at increasing the inclusion of representative populations throughout all phases of drug development. Most recently, FDA released a landmark guidance in June 2024 titled *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (489). This guidance fulfills a mandate of the Food and Drug Omnibus Reform Act of 2022 and builds upon earlier drafts by offering a more detailed and actionable framework. It required sponsors of certain clinical trials to submit Diversity Action Plans outlining specific enrollment goals for underrepresented populations and the strategies to achieve and track those goals. Complementing these efforts, Project Pragmatica promotes simplified trial designs that minimize participant burden and complexity while maintaining scientific rigor. These pragmatic trials offer more generalizable findings and support broader participation (1129).

Reflecting on the past 15 years reveals that equity in clinical trial participation has evolved from a conceptual goal to a foundational principle embedded in cancer drug development. Still, persistent gaps remain. Continued modernization of the clinical trial ecosystem is essential to ensure that all individuals affected by cancer, regardless of race, age, geography, or socioeconomic status, can access and benefit from clinical research. As the cancer research community looks to the future, building a truly inclusive and patient-centered clinical trial infrastructure remains both a scientific necessity and an ethical imperative.

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 (see **Sidebar 27**, p. 90). As a result, many patients with cancer are living longer and fuller lives after diagnosis. A key concept that has facilitated this progress is an increasing focus on personalized medicine, whereby knowledge of patient characteristics is leveraged to ensure maximal safety and efficacy for a specific drug in a specific patient (see **Figure 7**, p. 47).

Biomarker testing has fueled this personalized medicine revolution by identifying patient-specific characteristics that inform therapeutic selection. Precision therapies, or drugs requiring pre-treatment biomarker testing to select patients most likely to benefit, account for over 50 percent of all oncology drugs approved between 1998 and 2024, with the percentage increasing to over 61 percent in the past 5 years (1130). This percentage is likely to increase as more potential drug targets are identified, and more drugs are developed against known targets.

There are many recent examples of biomarkers being centered in drug development for the benefit of patients. For example, multiple meetings of FDA's Oncology Drug Advisory Committee (ODAC) this year have highlighted the use of biomarkers to select patients who will benefit most from specific treatments. Recent decisions have recommended

against expanding the indication of certain therapeutics from biomarker-defined patient populations to all patients with certain cancers or have recommended the restriction of therapeutics initially approved for biomarker-agnostic populations towards biomarker-defined ones (1131,1132).

Additionally, FDA has become increasingly aware of pharmacogenomic biomarker testing to increase patient safety by optimizing dosages and preventing adverse events. One long-standing area of interest for OCE was DPD deficiency (see **Advances in Treatment With Chemotherapy**, p. 105). Patients with DPD deficiency have an increased risk of severe and fatal toxicities upon receipt of fluoropyrimidine chemotherapies, which led FDA to update the labels for the fluoropyrimidines, capecitabine and 5-fluorouracil, in 2022 and 2024, respectively, to encourage health care providers to counsel patients about testing for this deficiency prior to initiating treatment with fluoropyrimidines (1133,1134). To encourage further awareness of this issue, FDA released a first-of-its-kind safety announcement highlighting the risks of treating patients with DPD deficiency with fluoropyrimidines (572). FDA also issued a request for public comment and partnered with AACR to host a workshop focused on the data patients and health care providers should consider when deciding whether to undergo DPD testing, interpreting test results, and determining appropriate next steps (1135,1136).

FDA has kept pace with innovation in oncology drug development, despite ongoing regulatory uncertainties in recent years. A 2025 analysis found that nearly 95 percent of novel oncology therapies received FDA approval before approval by the European Medicines Agency (EMA), reflecting both sponsors' tendency to submit first to FDA and the agency's significantly shorter average review timelines—by more than 200 days (1137).

This efficiency stems from FDA's long-standing priority to speed up the approval of treatments for serious conditions through expedited review programs, including its flagship Accelerated Approval pathway, established in 1992. This program allows for earlier approval of drugs that address unmet medical needs by relying on surrogate markers reasonably likely to predict clinical benefit (1138). 226 oncology drugs have been approved through the Accelerated Approval pathway since its inception, including notable drugs such as pembrolizumab, imatinib, and trastuzumab, thereby reaching patients and saving lives faster (1138).

While the Accelerated Approval pathway increases patient access to innovative therapeutics—on average 3.1 years before their own approval through the traditional pathway—it also introduces uncertainty (1139). Since drugs receiving accelerated approval do not have confirmed clinical benefit, there is a risk that patients are exposed to unsafe therapies that may ultimately not improve patient outcomes. This risk is mitigated by requiring subsequent large confirmatory clinical trials to validate their expected clinical benefit. Unfortunately, not all treatments approved through this pathway have shown real-world patient benefit, leading to their withdrawal from the market. In other cases, confirmatory trials are not initiated or completed in a timely manner, further increasing the associated uncertainties and potential risks.

To remedy this, the Food, Drug, and Cosmetic Act was amended in 2023 to grant FDA new authorities, including the ability to impose additional conditions on confirmatory studies and to expedite withdrawal of products that do not meet post-approval requirements. One key authority allows FDA to require that a confirmatory trial is underway at the time of accelerated approval, ensuring timely evaluation of a therapeutic's benefit. In 2025, FDA issued a new draft guidance delineating how it would implement these new authorities (1140,1141). Of particular note, FDA defined the term "underway" to mean that patient enrollment has begun, and the trial has a target completion date. In some cases, FDA may even require the trial to be fully enrolled.

Complementing these regulatory updates, FDA also announced the launch of the Commissioner's National Priority Voucher (CNPV) program—a new initiative designed to incentivize the development of therapies that address urgent public health needs. By offering expedited review vouchers for qualifying products, the CNPV program seeks to accelerate access to high-priority treatments, while reinforcing the FDA's commitment to protecting and advancing the health interests of the American people (1142).

Regulatory Collaboration and Global Harmonization

Regulatory collaboration and global harmonization have become essential pillars in accelerating the development and delivery of safe, effective cancer therapies worldwide. These efforts reflect a shared understanding that health challenges, especially cancer, do not recognize borders. 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 Harmonization (ICH), the International Pharmaceutical Regulators Program (IPRP), and the International Coalition of Medicines Regulatory Authorities (ICMRA) (1143). A key example is Project Orbis, launched in 2019 by OCE. Designed to enable concurrent submission and review of oncology drugs across multiple countries, Project Orbis has

Project Asha: Advancing Global Solutions in Health Care Access

Project Asha, launched in 2024, aims to expand oncology clinical trial access in India. The initiative supports locally relevant, patient-centered research while promoting global data sharing and more inclusive participation in cancer research. Project Asha focuses on clinical research training and pragmatic, patient-centered trials tailored to low-resource settings, with support from Indian pharmaceutical partners.

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established a structured pathway for collaborative, cross-border evaluation of cancer therapies, reducing delays and enabling more patients to benefit from lifesaving treatments sooner. FDA, in collaboration with the Australian Therapeutic Goods Administration (TGA) and Health Canada (HC), conducted the first Project Orbis review (1144). Since then, Brazil, Israel, Singapore, Switzerland, and the United Kingdom have joined as partners. In 2024 alone, 23 oncology products were approved through Project Orbis, bringing the total to 112 approvals to date (1145).

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. As FDA and its international partners continue to expand these efforts, the future of cancer care will be shaped by enhanced representation, shared innovation, and faster delivery of life-saving cancer treatments.

Advancing Policies to Strengthen Cancer Prevention and Screening Programs

Nearly 40 percent of cancer cases in the United States can be attributed to preventable risk factors, such as tobacco use, dietary factors, and ultraviolet (UV) exposure (see **Reducing the Risk of Cancer Development**, p. 51). 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. 71). In fact, 80 percent of the lives saved from five of the most common cancers over the past 45 years have been the result of advances in prevention and screening (67). However, inequities in access to screenings and follow-up care contribute to health disparities and lower chances of survival in some patient populations (see **Effective Strategies Increase Screening Uptake**, p. 78). Innovative and inclusive screening practices, from both health care providers and policymakers, are necessary to improve overall cancer prevention and screening rates. Digital health tools can improve cancer screening access and outcomes for populations with limited health care access, particularly those residing in rural areas (1146). For states like Alabama, where 55 of their 67 counties are rural, equitable access to these lifesaving measures remains a focus for **Senator Katie Britt (R-AL)** (see p. 219). In addition, targeted outreach with supportive patient navigation services can also boost cancer screening participation in rural populations (1147). Increased investment in Federally Qualified Health Centers will further improve capacities to address the unmet cancer screening needs in the US population (1148).

A significant barrier to cancer prevention and screening services is the associated cost and lack of insurance coverage for many individuals. The Affordable Care Act (ACA) of 2010 required private insurers and Medicaid expansion programs to cover recommended cancer screenings (e.g., mammograms, Pap tests, colonoscopies, and lung cancer screening) without patient cost-sharing. Future legislation such as H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act introduced by Representative Terri Sewell (AL-07) and Representative Jodey Arrington (TX-19), would allow for multi-cancer early detection (MCED) tests to be covered by Medicare in a timely manner upon approval by FDA, enhancing cancer screening rates across a broader population (1149). Expansion of health insurance through Medicare/Medicaid and growth of ACA marketplace plans will also improve access to preventive services, cancer screening, and early detection. Importantly, for some cancers, screening rates remain below pre-COVID-19 pandemic levels and will require additional interventions (1150). Continued progress in the fight against cancer will rely heavily on eliminating the inequities that exist in the prevention, screening, and early detection of cancer.

Mitigating Preventable Risk Factors

Research has shown that modifying certain health behaviors and other lifestyle choices can reduce the risk of cancer. Human papillomavirus (HPV) can cause several cancers,

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THE HONORABLE
Katie Britt
US SENATOR FROM ALABAMA

Which policy priorities or legislative efforts are you most proud of that help advance cancer prevention, early detection, treatment, or patient care?

"I've been grateful to work on a specific piece of legislation, the Access to Breast Cancer Diagnosis Act, or the ABCD Act, with Senator Jeanne Shaheen of New Hampshire in both the 118th and 119th Congresses. We know that it's critical for women to be screened and diagnosed as soon as possible to give them the widest variety of treatment options and the best chance to defeat this disease. Our bipartisan legislation would ensure that a warranted follow-up diagnostic examination is also covered by health insurers with no out-of-pocket cost to the patient. It's estimated that 1 in 8 women will be diagnosed with invasive breast cancer in their lifetime. In my home state of Alabama, around 4,500 women were diagnosed in 2023. Diagnostic tests, which are necessary in about 10 percent of cases, can cost patients hundreds of dollars. No woman across America should not be able to confirm whether she has a life-threatening illness when the resource is readily available. I believe this is commonsense legislation, and I'm proud to champion it in the Senate."

What message would you like to share with the scientists, clinicians, and patient advocates working every day to make progress against cancer?

"Thank you. Your work keeps our children safe, our families strong, and our communities thriving. In Alabama, we are so incredibly proud of the University of Alabama at Birmingham's O'Neal Comprehensive Cancer Center. The researchers and doctors at UAB O'Neal give patients and families hope—not just in Alabama, but across our nation as one of our preeminent comprehensive cancer centers. As the O'Neal Center continues to pioneer lifesaving research, advance innovative treatments, and deliver world-class care, I'm proud to support its mission of bringing hope to families and communities with the ultimate vision of a life without cancer. We have seen encouraging steps forward—from new immunotherapies to breakthroughs in early detection—but there is still so much more to do. My commitment to being a partner on the federal level extends to all of the incredible researchers, doctors, and advocacy groups who work diligently to support those who have been affected and those who might one day receive a cancer diagnosis. You have all made extraordinary contributions to patients, to finding cures, and to the future of medicine."

Bipartisan support for cancer research has been a hallmark of progress over the past several decades. Why do you believe this issue continues to bring both parties together and why must that commitment continue?

"Cancer has tragically touched the lives of so many—a majority of Americans have been affected by this deadly disease. I believe Congress has a duty to ensure we continue to support lifesaving and life-changing research. At the federal level, I've been grateful to work with a number of my colleagues in a bipartisan fashion to advocate for continued investment in cancer research to innovate and save lives moving forward. I believe this sustained federal support is critical to developing innovative treatments and finding cures for all types of cancer. Ultimately, treating and defeating cancer is not a partisan issue. The fight against cancer deserves unity across the aisle to ensure progress continues so every American—regardless of zip code—can benefit from the very best in cancer care."

As scientific innovation accelerates, what opportunities do you see on the horizon for improving outcomes for cancer patients in the United States, particularly in rural or underserved communities?

"In Alabama, 55 of our 67 counties are rural. Access to high-quality healthcare across rural communities remains a top priority of mine. I have been proud to work with many of my colleagues on both sides of the aisle to advance solutions to support families in every corner of our nation. I joined Senators Maggie Hassan of New Hampshire, Susan Collins of Maine, and Tina Smith of Minnesota to introduce the Rural Obstetrics Readiness Act. Our legislation would equip rural hospitals with the tools, training, and resources to deliver urgent obstetric care. We would help medical professionals prepare to handle obstetric emergencies that come through their doors and ensure women have access to high-quality care throughout their pregnancy journey, no matter their zip code. Additionally, telehealth has become an indispensable resource for countless communities—I'm committed to advancing legislation that expands access to telehealth services. It's imperative we support the ability of our healthcare workers and medical providers to reach and treat more hardworking families in every corner of America. I'll continue to work diligently at the federal level to support timely and accessible healthcare solutions."

"It's devastating that nearly 25,000 people die from cancer every year in Illinois alone. I'm proud to have led bipartisan legislation to expand Medicare coverage for breast cancer patients and survivors, as well as legislation to expand access to cancer screenings and related care for our Veterans. Despite this Administration's unacceptable meddling in cancer research funding, expanding cancer research and access to care should never be a partisan issue. I remain committed as ever to working with my colleagues on both sides of the aisle to help provide doctors and researchers with what they need to keep making breakthroughs so we can find cures and save lives."

The Honorable Tammy Duckworth
US Senator from Illinois

including nearly all cases of cervical cancer (see **Prevent and Eliminate Infection From Cancer-causing Pathogens**, p. 64). Effective strategies are available to prevent HPV infection and its associated cancers, including vaccination, targeted screening, and timely follow-up care. HPV vaccination rates have increased among adolescents, though more still needs to be done to reach the Healthy People 2030 goal of an 80 percent vaccination rate among adolescents (1151). Models have shown that HPV vaccination levels significantly vary across states and tailored approaches are needed to identify and address local barriers to coverage (1152).

Although progress has been made in HPV prevention, other cancer prevention efforts still fall short in addressing other major risk factors. For example, the current strategy notably lacks a focus on tobacco control—still the leading preventable cause of cancer. Comprehensive cancer prevention must also address other critical determinants of health, including alcohol consumption, environmental exposures, and structural inequities that shape access to healthy choices.

Improving Screening Guidelines and Risk-based Approaches

The US Preventive Services Task Force (USPSTF) routinely evaluates and updates cancer screening guidelines (see **Sidebar 24**, p. 75). To address the rising cancer incidence in young adults, the USPSTF updated its guidelines in 2021 to recommend colorectal cancer screening for adults with average risk to 45 to 75 years instead of 50 to 75 years and in 2024 to recommend breast cancer screening using biennial mammography for women ages 40 to 74 years instead of 50 to 74 years. In December 2024, the USPSTF released draft changes to cervical cancer screening recommendations that include the addition of patient-collected high-risk HPV primary screening in women ages 30 to 65 years (1153).

Currently, eligibility for population-based cancer screening programs is primarily based on age and sex. Personalized risk-based screening (PRBS) for cancer is an emerging approach that considers individual risk factors such as genetics, environmental exposures, 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 (1154). PRBS is gaining traction as the potential next step for cancer prevention and control among both the general public and health care community (1155). The development of artificial intelligence (AI)–based tools has enhanced the ability to utilize personalized preventive medicine techniques such as PRBS. Application of AI algorithms can effectively stratify cancer risk within the general population and shift patients from general to targeted cancer screening (see **Advances in Artificial Intelligence (AI)**, p. 82) (1156). Furthermore, the use of AI-based predictive models could define cancer prevention strategies by giving patients a greater understanding of their personal risk factors and the importance of appropriate screening, even for cancers that currently have no screening guidelines (1157). These findings have fueled a shift towards PRBS to enhance the value of cancer screening; however, implementation strategies and policies are needed to address the barriers at the individual, provider, and health care system levels as well as challenges with algorithmic bias and validation of predictive models.

Cancer Prevention and Screening Programs

CDC plays a key role in promoting cancer screening and addressing cancer screening disparities as well as educating the public about cancer prevention. CDC's DCPC runs critical programs to increase overall cancer screening rates including the NBCCEDP, National Comprehensive Cancer Control Program (NCCCP), and CRCCP. DCPC has public health campaigns that help educate people on cancer risks, including targeted outreach to those with higher risks and medically underserved populations (see **Sidebar 59**, p. 221). CDC also compiles and provides Cancer Screening Change Packages as a resource for clinical teams to support the delivery of cancer screening services. CDC released its first set of Cancer Screening Change Packages in the summer of 2023 and released a breast cancer screening change package on July 16, 2024 (1158).

SIDEBAR 59

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 18–44), 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.

Source: (1162).

Within CDC, the National Institute for Occupational Safety and Health (NIOSH) plays an important role in identifying carcinogenic hazards, tracking occupational cancer risks, and developing mitigation strategies. NIOSH maintains the List of Hazardous Drugs in Healthcare Settings, last updated in December 2024, that includes carcinogens (1159). This function is essential to cancer prevention efforts in the broader population.

Sustained progress towards increasing overall cancer screening rates requires continued investment in CDC and support for legislation like H.R.2381, SCREENS for Cancer Act of 2025, introduced by Representative Joseph Morelle (D-NY-25), which would reauthorize and improve the NBCCEDP for FY 2026 through 2030 (1160). Furthermore, renewed support for CDC programs and initiatives would help meet future cancer screening goals including the NBCCEDP aim to increase the percentage of women who receive overdue cervical cancer screening from 20 percent to 35 percent by 2026 (1161).

Leveraging Policy to Reduce Tobacco-related Illness

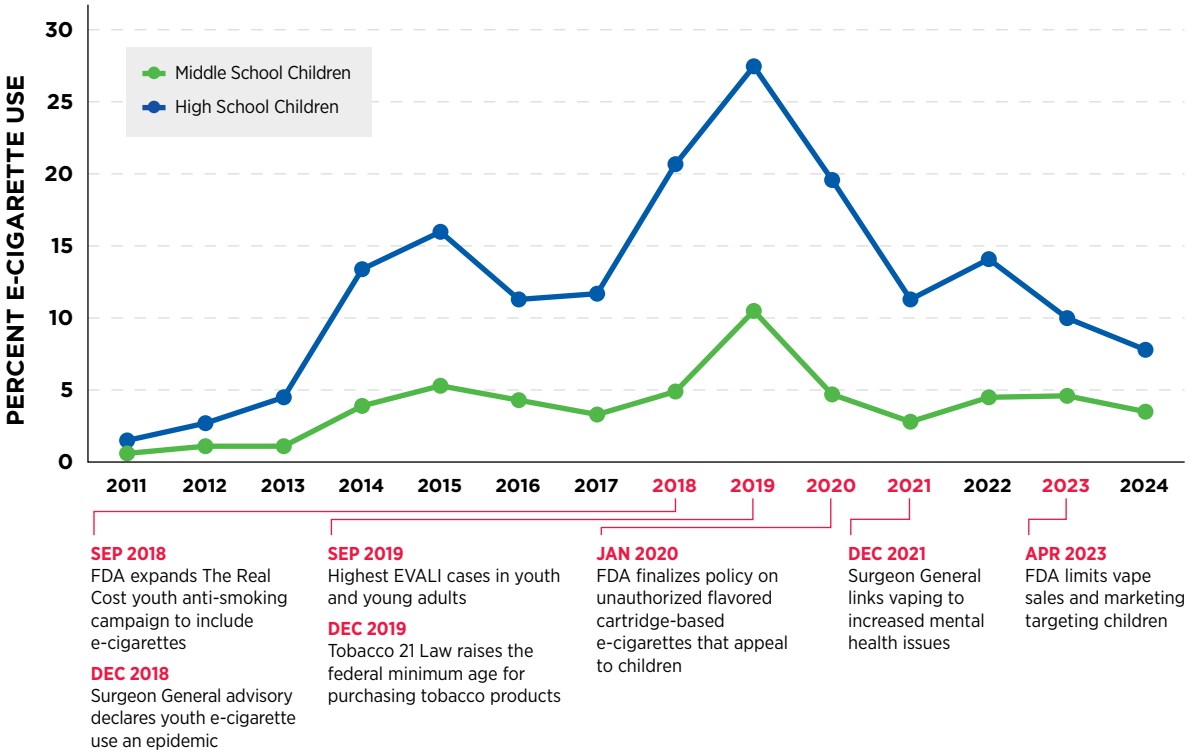
Tobacco use remains the leading cause of preventable cancers and is linked to 17 different types of cancers, in addition to lung cancer, which is the number one cause of cancer deaths in the United States (see **Eliminate Tobacco Use**, p. 53). Nearly half a million Americans die from cigarette smoking annually, with over 7,000 Americans dying from lung cancer related to secondhand smoke. This does not include the approximate 34,000 annual deaths from heart disease from secondhand smoke (1163,1164). Currently, approximately 28.8 million adults smoke cigarettes (1165). Additionally, due to predatory marketing campaigns from the tobacco industry, tobacco use remains higher in certain communities, including Black individuals and Native Americans (1166). Members of the LGBTQ+ community also smoke tobacco at a higher rate than heterosexual/straight adults (15.3 percent compared to 11.4 percent) (1167).

However, despite these grim statistics, notable progress has been made in both tobacco prevention and cessation, particularly among youth. While 2.25 million youth still use tobacco products, the rate of youth cigarette smoking is at a 25-year low (189). These landmark numbers are a sign of progress and show the success of national anti-smoking and nicotine programs coordinated by both federal and non-federal entities, such as the recently launched Outsmart Nicotine campaign (1168) and the long-standing 1-800-QUIT-NOW helpline (1169). Therefore, while there is still progress to be made, overall cigarette smoking rates have continued to fall (1165).

At the peak of the electronic cigarettes (e-cigarettes) epidemic in 2019, 31 percent of high school students and 12.5 percent of middle school students reported current use of a tobacco product, with the vast majority of use consisting of e-cigarettes (1170). In 2024, these rates fell to 10.1 percent and 5.4 percent, respectively, driven by major decreases in e-cigarette use (1171). In fact, youth e-cigarette use reached its lowest level in a decade, with 5.9 percent of youth reporting current use. These successes resulted in large part from swift policy action

FIGURE 26

Federal Programs Contribute to Decreasing E-cigarette Use Among Youth



E-cigarettes exploded in popularity prior to the pandemic, reaching their 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 against illegal e-cigarettes, and new policies and laws have helped to curtail the youth e-cigarette epidemic. Additional new policies and efforts, funded by federal programs at centers like the CDC Office on Smoking and Health and the FDA Center for Tobacco Products, will be necessary to continue decreasing youth e-cigarette use.

CDC, Centers for Disease Control and Prevention; DOJ, US Department of Justice; EVALI, e-cigarette or vaping product use–associated lung injury; FDA, US Food and Drug Administration.

and federal funding for e-cigarette prevention programs and should be celebrated (see **Figure 26**, p. 222).

Unfortunately, no tobacco product is safe and tobacco product use remains the leading cause of preventable disease and death in the United States. While tobacco use is generally decreasing, nearly 20 percent of adults still report use of any tobacco product and 14.6 percent report use of combustible tobacco products, the most harmful type of product (1172). In the face of massive cuts and reorganization to federal tobacco control and regulation organizations including CDC's Office of Smoking and Health (OSH) and FDA's CTP, it is imperative to highlight the successes of these organizations and continue pushing for and implementing innovative tobacco control policies and research to further drive the decline in tobacco use (1173).

Flavored Tobacco Products

Evidence-based policies that address the evolution of tobacco products to include new additives and flavors are needed to reduce tobacco-related illness and health disparities. While cigarettes with characterizing flavors other than menthol were nationally prohibited in 2009, the addition of flavors to tobacco products remains prevalent. Menthol cigarettes and

flavor additives in other combustible and non-combustible products remain common. This increases their appeal, is associated with greater rates of cigarette initiation, facilitates sustained use, and decreases rates of successful cessation, particularly among youth (1174). As a result of the substantial scientific evidence supporting prohibition of menthol and other flavors in tobacco products, FDA proposed draft rules in 2022 that would ban menthol as a characterizing flavor in cigarettes and all characterizing flavors, including menthol, in cigars. However, on January 21, 2025, the proposed rule was withdrawn (1175). Currently, multiple states and localities have implemented restrictions on flavored tobacco products (1176). Notably, while there has been state and local adoption of limitations on flavored tobacco products, these policies have primarily targeted electronic nicotine delivery systems (ENDS) and non-combustible tobacco products (1177). Novel regulatory approaches to banning flavors in tobacco products are needed to realize the tremendous potential public health benefits. Comprehensive policies that prohibit flavors as well as ingredients or additives that affect sensory properties would close possible loopholes and better achieve the intended health outcomes (1178). In addition, research is needed to identify effective public health messaging for flavored tobacco products to prevent use initiation, promote cessation, and advance harm reduction. Robust policies that restrict both flavored tobacco product sales and marketing contribute to lower levels of adolescent exposure to flavored tobacco product advertising and may reduce product use (1179). Reducing the addictiveness of tobacco products by prohibiting flavors and sensory modifiers would help prevent tobacco-related cancers and save millions of lives in the coming decades.

Funding Federal Regulatory, Enforcement, and Control Activities

FDA's tobacco regulatory and enforcement activities, helmed by CTP, are entirely funded by user fees charged to manufacturers and importers of certain tobacco products. However, unlike all other tobacco product manufacturers, ENDS (e.g., e-cigarettes) manufacturers currently do not pay user fees to FDA. The bipartisan-supported Resources to Prevent Youth Vaping Act (S. 3653) was introduced in the 118th Congress to authorize FDA to begin collecting user fees from e-cigarette manufacturers and would provide FDA's CTP an additional $100 million in funding per year, but no further legislative action has occurred (1180). Requiring e-cigarette manufacturers to pay user fees to FDA will be critical to supporting efforts to control tobacco use, including enforcement actions against illegal products, as CTP currently experiences an outsized workload related to these products. Despite this gap in funding, FDA's CTP has recently made strides across four key areas it manages: regulation and guidance, compliance and enforcement, science and research, and public health education.

FDA CTP's regulatory efforts are multifaceted, including product approvals and rulemaking, among other roles. FDA CTP has received an unprecedented number of premarket tobacco applications (PMTAs), submitted by tobacco companies seeking authorization to sell their products, having processed over 26 million out of the total 27 million applications submitted (1181). While the vast majority have led to marketing denial orders, some products have been authorized. In particular, there are now 34 FDA-authorized e-cigarette products, and marketing authorization was recently granted to a novel nicotine pouch product (1182,1183). Although these products pose health risks, as do all nicotine products, FDA determined that the benefits of these products outweigh the risks to the population as a whole. When authorizing new tobacco products, FDA scrutinizes the potential benefit of completely switching to the new product for adults who use cigarettes and/or other smokeless tobacco products, as these products are expected to confer lower risk of cancer and other tobacco-related illnesses. This is balanced against the risk of new users, including youth, who may begin to use the new products. FDA continues to monitor these decisions in the post-market setting to ensure that they meet the necessary public health standards. Additionally, FDA finalized guidance outlined by legislation in 2019 to prohibit the sale of tobacco products to those younger than 21 years of age. While this law has been in effect since 2019, this recent finalization brings FDA regulation into line with legislation and signifies FDA's commitment to preventing youth tobacco use (1184). FDA has also proposed a rule that would reduce nicotine levels in many combustible products by 95 percent. If finalized, this rule is projected to cause nearly 13 million people to quit smoking within one year, prevent 1.8 million tobacco-related deaths by 2060, and save more than $1.1 trillion (1185).

FDA has also recently increased its enforcement efforts to prevent unauthorized illegal tobacco products from being sold. Last year, an FDA-Department of Justice task force was created to curtail the massive illegal e-cigarette marketplace, which constitutes 86 percent of all e-cigarette products and includes nearly all flavored products (1186,1187). Enforcement actions have ramped up since the creation of this task force, seizing millions of dollars of products, issuing warning letters, and seeking fines (1188). However, most of these actions have been limited to smaller or foreign organizations and have not yet substantially impacted this multibillion-dollar market.

Federal educational campaigns to prevent tobacco initiation have also come to fruition. Exposure to FDA's The Real Cost e-cigarette prevention campaign was directly correlated with decreased likelihood of reporting e-cigarette initiation and prevented an estimated 450,000 youth from initiating cigarettes between 2023 and 2024 (1189). CDC OSH's Tips from Former Smokers (Tips) campaign was also significantly associated with calls to federal quit lines, generating an estimated 2.1 million calls between 2012 and 2023, or nearly 25 percent of all calls (1190).

In addition to the Tips campaign, CDC OSH's other programs have significantly contributed to the protection of the American public from the harms of tobacco use. OSH tracks tobacco product use and analyzes changes in tobacco-related disease incidence, including contributing to the yearly National Youth Tobacco Survey (1171) alongside FDA CTP, providing essential longitudinal insight into how youth are interacting with tobacco products and how to curb future use. CDC OSH also supports all state tobacco control programs through their National and State Tobacco Control Program (1191), which provides funding, increases reach and accessibility, and supplies expertise and technological support. CDC OSH is set to fund state tobacco control programs for nearly $70 million in the 2024–2025 year (1191). Historically, every $1 spent on these programs leads to a $55 return on investment in averted health care costs (1192), highlighting the significant costs of tobacco-related chronic disease and the incredible benefits of a strong CDC OSH.

The efforts outlined here, spanning regulation, education, and research, highlight the importance and impact of funding for federal tobacco-related programs. While these programs have generated tangible health benefits for the American public, their futures remain uncertain. Additional policies supported by these programs that could reduce tobacco-related illness include improved insurance coverage for evidence-based smoking cessation therapies; further restrictions on tobacco product advertising and promotions; and increased funding for FDA, NCI, and CDC smoking awareness, research, and cessation programs. As highlighted by the 2024 US Surgeon General's Report, *Eliminating Tobacco-Related Disease and Death*, though there has been much progress in tobacco control, tobacco remains a major cause of death and poses an outsized danger to vulnerable populations. Efforts proposed in the Surgeon General's Report to eliminate the burden of death and disease resulting from tobacco use include further restrictions to flavored products and consumer marketing of tobacco products as well as the implementation of the proposed rule for nicotine reduction (1193).

Addressing Cancer Disparities and Improving Patient Outcomes

As described in the *AACR Cancer Disparities Progress Report 2024* (12), cancer and other health disparities are driven by a complex set of interrelated causes, including social, economic, and environmental factors—collectively known as social determinants or social drivers of health (SDOH) (see **Figure 3**, p. 22) (1194). Addressing the negative impact of SDOH is essential for achieving health equity and will continue to require multifaceted solutions, including new policies at the federal, state, and local levels, as well as collaboration between policymakers, health care providers, and patients.

Environmental Justice and Cancer

Within SDOH, environmental factors remain an ongoing subject of discussion on how marginalized communities can face increased cancer risks. Environmental justice as a movement arose in response to a disproportionate exposure of harmful pollution, toxic sites and facilities, and other carcinogenic factors. The "Cancer Alley," a regional nickname for a stretch of land between Baton Rouge and New Orleans, Louisiana, is home to over 150 oil refineries, plastic plants, and chemical facilities (1195), and has a 40 percent Black population, as compared with the national 12 percent average. Given the petrochemical environment, which has ramifications for both quality of life and for health outcomes, and other factors, the risk of cancer in "Cancer Alley" is 95 percent higher than in most of the country (see **Limit Exposure to Environmental Risk Factors**, p. 67) (1196).

Environmental justice is not limited to geographic factors, with matters like economic status also impacting health outcomes. In older housing environments, exposure to lead in paint, dust, and pipes has resulted in one in five children in these homes having higher blood lead levels (1197), as compared to one in eight in other settings. Communities impacted by environmental factors deserve additional resources in prevention, screening, and treatment. Addressing these externalities must remain a priority for policymakers, to ensure no one faces a higher risk due to environmental factors.

Patient-centered Care and Outcomes and Survivorship

As cancer research continues to improve overall detection and treatment, there are millions of cancer survivors. As of January 2022, an estimated 18.1 million cancer survivors live in the United States, including nearly 500,000 who were diagnosed before the age of 20 (9), underscoring the impact of sustained investment in research. As more people survive cancer, the need to study the long-term health of these survivors continues to grow, particularly for pediatric survivors whose treatment options are more likely to have many more long-term consequences (see **Addressing the Unique Challenges Faced by Vulnerable Populations**, p. 181). Policies like the Childhood Cancer STAR (Survivorship, Treatment, Access, Research) Act, which saw bipartisan sponsors, including Co-Chair of the House Cancer Caucus **Representative Mike Kelly (R-PA)** (see p. 225), help provide researchers with the tools to better address these research gaps.

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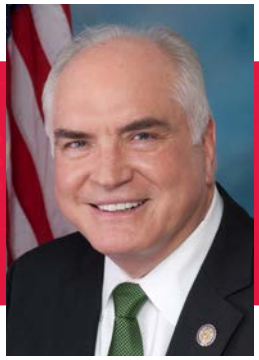

THE HONORABLE
Mike Kelly
US REPRESENTATIVE FOR PENNSYLVANIA'S 16TH DISTRICT

Cancer has touched so many lives. Could you share how it has impacted you personally, or someone close to you?

"Like so many other American families, cancer has impacted our family, as well. Their stories and their battles guide my work in Congress, to work toward a day when no one has to hear they have cancer."

How has that personal experience influenced your work in Congress, particularly around health policy and the importance of funding for cancer screening, prevention, and research?

"It's always tough to watch family members battle cancer. Their personal battles with cancer are always top-of-mind as we work on legislation in Congress. Much of the work we do on the bipartisan House Cancer Caucus focuses on prevention and research. We work to bring new cancer treatments to the market to give patients a greater chance at beating cancer."

Which policy priorities or legislative efforts are you most proud of that help advance cancer prevention, early detection, treatment, or patient care?

"I'm particularly proud of the legislation we have passed regarding pediatric cancer to help America's children, including the STAR Act. This legislation expands research on childhood cancers and works to enhance the quality of life for survivors. Through bipartisan efforts and teamwork, we were able to get this bill over the finish line. Before I began serving in Congress, I was an automobile dealer, including a Hyundai dealer. I've had the chance to work with Hyundai Hope on Wheels, which raises money for pediatric cancer research. I've had the chance to meet so many young, brave cancer patients. Their stories inspire me every day."

What message would you like to share with the scientists, clinicians, and patient advocates working every day to make progress against cancer?

"First, thank you for the work you're doing. Without you, without the men and women who work day in and day out to find a cure, we wouldn't be able to discover some of the incredible scientific breakthroughs that have led to improved treatments and better patient outcomes. I also want to thank our patient advocates, including the wonderful Hyundai Hope on Wheels Youth Ambassadors who I've had the honor of working with over the years. Your efforts continue to lead to medical breakthroughs and support in Congress."

Bipartisan support for cancer research has been a hallmark of progress over the past several decades. Why do you believe this issue continues to bring both parties together and why must that commitment continue?

"Cancer is something that impacts all of us. It's not a red issue or a blue issue. It's a red, white, and blue issue. In a political climate where so much can be divided, members of Congress from both sides know this issue isn't political at all. It requires all of us to come together for a common cause."

As scientific innovation accelerates, what opportunities do you see on the horizon for improving outcomes for cancer patients in the US, particularly in rural or underserved communities?

"I'm hopeful that one day, no one will have to hear the words 'you have cancer.' I really believe that one day we can get there. We have already taken steps this year and in recent years. In his first term, President Trump signed the Right-to-Try law, which allows Americans battling cancer and other diseases to receive early access to experimental drugs as they pursue a solution that is best for them. The House Cancer Caucus has also supported the FDA's ban of Red Dye No. 3 earlier this year. Specific to our rural communities, expanding telehealth options remains a priority of mine, not only for cancer patients but for all medical needs. The caucus is dedicated to eliminating cancer as a public health threat."

Quality cancer care includes survivorship, and continued research investments in this area are essential for overall health. Patient-centered care can improve overall survival quality of life, for both the survivor and their support system. Both the physical and mental health of cancer survivors should remain an integral part of holistic cancer research. CDC supports cancer survivors by providing resources with nuanced tools for all stages of survival—including factors like hair loss (1198) and stress mitigation tools for the post-treatment period.

For so many pediatric cancer survivors and their support systems, returning to a sense of normalcy can be complex and often includes late effects of treatment (1199). Tools like the NCI's Childhood Cancer Data Initiative (CCDI) (1200) can help researchers access necessary information to improve survivorship and mitigate negative side effects. The Children's Oncology Group (COG), which is a member of the NCI's National Clinical Trials Network (NCTN), is the world's largest organization devoted exclusively to childhood and adolescent cancer research. COG has more than 100 active clinical trials. There are approximately 12,000 patients registered on COG trials each year. These trials include front-line treatment for many types of childhood cancers, studies aimed at determining the underlying biology of these diseases, and trials involving new and emerging treatments, supportive care, and survivorship. (1201,1202).

Improving the Use of Digital Information in Cancer Treatment and Management

To improve the delivery of care to patients and improve outcomes for survivors, it is critically important to expand the use of digital health information, including making health registries more robust, timely, and inclusive of information beyond what they currently collect. There is an accompanying need to standardize the collection, security, and dissemination of this information for patients, caregivers, clinicians, and researchers. Although progress has been made in the expansion of electronic health records and telemedicine, opportunities to maximize the benefits of digital health care technologies in oncology have been growing (1203). For example, patient information is often stored across multiple databases, depending on the systems used by a patient's health care providers, pharmacies, and insurers. Tracking patient data, including patient reported outcomes, is therefore incredibly difficult, hampering effective care (1204). There are also significant shortcomings in the collection and systematic organization of different types of potentially relevant patient data, including the patient's race and ethnicity, sexual orientation and gender identity, patient reported outcomes of cancer therapy, and diagnostic results (1203,1204).

Federal investments in programs like NCI's CCDI (1200) underscore how increased data sharing can better improve overall treatment and survivorship. CCDI is tasked with gathering data on every child, adolescent, and young adult with a childhood cancer diagnosis and with developing a platform to share the research data involved in their treatment. Having shareable data on rare pediatric cancers, which are often hard to diagnose and lack standardized care, can help improve both outcomes and survivorship.

AACR Call to Action

Sustained Progress Requires Sustained Commitment

The extraordinary achievements detailed in this and the previous 14 editions of the *AACR Cancer Progress Report* are the direct result of more than 50 years of strategic, bipartisan investment in medical research. These efforts have transformed our understanding of the more than 200 different diseases we call cancer, accelerated the discovery of innovative treatments, and helped millions of people live longer, healthier lives.

This progress reflects a national commitment that has united policymakers across party lines behind the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA). For decades, research supported by these agencies has not only advanced our knowledge of cancer, but it has also transformed once-unimaginable hopes into tangible outcomes: more early detections, more effective treatments, and more time with the people we love. Patients are living well beyond their diagnoses, and families are seeing futures they once feared they would never see. These remarkable advances are the very outcomes made possible by sustained investment in science.

But all of that progress is now at risk.

A Growing Threat to Scientific Progress

The president's fiscal year 2026 budget would reduce NIH funding by nearly 40 percent. This unprecedented cut would devastate cancer research, derail scientific progress, and jeopardize future cures. Additional reductions targeting the National Cancer Institute (NCI) and the Advanced Research Projects Agency for Health (ARPA-H) would compound the damage, eroding the infrastructure that supports discovery and patient access to lifesaving advances. The president's proposal breaks with decades of bipartisan commitment and follows a year of funding constraints, policy changes, and administrative upheaval that have already destabilized the medical research enterprise.

One of the most alarming of these new policies is a sweeping executive order titled "Improving Oversight of Federal Grantmaking" issued in August that strikes at the foundation of American science. It gives political appointees extraordinary authority to override expert peer review, retroactively cancel previously awarded research grants, and reshape funding priorities based on ideology rather than evidence. This expansion of political control would dismantle the safeguards that have kept research independent for decades. In cancer research, it could mean halting a clinical trial for patients with no remaining treatment options simply because it no longer aligns with shifting political priorities, erasing years of work, wasting taxpayer dollars, and leaving patients without hope.

These new threats are striking a research system weakened by instability at the very institutions that drive medical progress. The damage is slowing discovery, disrupting care, and eroding confidence in the future of federally supported science. Without stability and sage direction, progress will stall, and patients will be left waiting, unsure if the answers they need will come in time.

Bottom line, the actions this administration is taking are dismantling an infrastructure that has enabled decades of progress and are abandoning our nation's historic commitment to science and the patients whose lives are at stake.

A Moment of Bipartisan Progress

Congress has the power and the obligation to protect the progress that science has made possible, and after months of uncertainty and escalating concern, Congress is beginning to respond. In late July, the Senate Appropriations Committee advanced a bipartisan bill that rejected devastating cuts to NIH and NCI and reaffirmed the importance of science in safeguarding the nation's health. The bill provides $47.2 billion for NIH and $7.374 billion for NCI, which includes increases of $400 million for NIH and $150 million for NCI. This action was a forceful rejection of policies that have delayed research, dismantled infrastructure, and weakened America's position as a global leader in medical innovation.

The bill includes critical provisions to block harmful administrative changes, defend scientific independence, and protect the foundation that enables lifesaving discovery. The leadership from Senators Shelley Moore Capito (R-WV), Tammy Baldwin (D-WI), Susan Collins (R-ME), and Patty Murray (D-WA) was instrumental in advancing this bill and reaffirming Congress's bipartisan commitment to science, patients, and the future of medical research. At a time of

deep division and political pressure, they demonstrated what responsible, forward-looking leaders can achieve.

But the crisis has not passed. Delays in NIH funding remain unresolved. Political interference continues. Research institutions are operating in a climate of fear and instability. The medical research community is counting on Congress to pass a full-year spending bill for NIH in fiscal year (FY) 2026, as opposed to agreeing to a full-year continuing resolution for FY 2026 that would extend funding for NIH through September 30, 2026, at the same level as FY 2025.

Congress Must Act

AACR urges Congress to take immediate action to:

- **Restart clinical trials and restore canceled research grants** to ensure that patients are not turned away from lifesaving studies and that promising science is not lost at a critical stage.
- **Support the federal research infrastructure** to repair the damage caused by mass reductions in workforce, frozen contracts, and suspended peer review. Discovery has stalled, and scientific capacity is breaking down.
- **Protect public health programs that prevent cancer** to avoid losing ground on screening, HPV vaccination, tobacco cessation, and early interventions. These efforts save lives.
- **Ensure that new treatments reach patients without delay** to prevent promising therapies from being trapped in bureaucratic limbo while families wait for help that may come too late.
- **Foster early-career and early-stage scientists and stabilize research careers** to stop the exodus of postdoctoral researchers and junior investigators who are abandoning science or being recruited overseas. When they leave, they take future cures with them.
- **Defend the independence and integrity of science** by reversing the August executive order that politicizes federal grantmaking, thus restoring safeguards that keep research free from political interference and ensuring that grantmaking, peer review, and public policies are guided by scientific evidence rather than ideology.
- **Reassert America's global leadership in medical innovation** to preserve decades of progress and ensure the United States remains at the forefront of the next generation of cures.
- **Provide no less than $51.303 billion for NIH and $7.934 billion for NCI in fiscal year 2026** to sustain the scientific workforce, power new breakthroughs against cancer and other human diseases, and uphold a national commitment to the patients and families who are relying on lifesaving progress.

The Path Forward

Cancer remains one of the most urgent and universal challenges of our time. It touches every family, every community, and every generation. For more than 50 years, the United States has led the world in confronting this disease through bold investment, bipartisan resolve, and a belief in the power of science to save lives.

At this pivotal moment, Congress must act. The future of cancer research depends on sustained federal investment, an independent and stable scientific enterprise, and policies that put patients first. What happens next will determine whether people receive the care they need, whether families find answers, and whether science continues to deliver hope to those who need it most.

We know what science can achieve when it is supported and allowed to flourish. We owe it to every patient, every survivor, and every family to protect the progress we have made and deliver on the promise of a future without cancer.

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Glossary

This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2025*. NCI has been used as the primary source for most definitions.

Acute myeloid leukemia (AML) A fast-growing cancer in which too many myeloblasts (a type of immature white blood cell) are found in the bone marrow and blood. Also called acute myelogenous leukemia.

Acute lymphocytic leukemia (ALL) A type of leukemia (blood cancer) that comes on quickly and is fast growing. In acute lymphocytic leukemia, there are too many lymphoblasts (immature white blood cells) in the blood and bone marrow. Also called acute lymphoblastic leukemia.

Adenocarcinoma Cancer that forms in the glandular tissue, which lines certain internal organs and makes and releases substances in the body, such as mucus, digestive juices, and other fluids. Most cancers of the breast, lung, esophagus, stomach, colon, rectum, pancreas, prostate, and uterus are adenocarcinomas.

Adjuvant therapy Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Angiogenesis The process of growing new blood vessels from the existing vasculature. Angiogenesis is important for numerous normal body functions, as well as tumor growth and metastasis.

Antibody–drug conjugate (ADC) A therapeutic comprising an antibody chemically linked to a cytotoxic chemotherapeutic. The antibody binds to specific proteins on the surface of certain types of cells, including cancer cells. The linked cytotoxic chemotherapeutic enters these cells and kills them without harming nearby cells.

Artificial intelligence (AI) A phenomenon that leverages computers and machines to mimic the problem-solving and decision-making capabilities of the human mind, such as how to act, reason, and learn.

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

B-cell maturation antigen (BCMA) A receptor that plays an important role in regulating B-cell proliferation and survival. BCMA is expressed on the cell membrane of normal and malignant plasma cells, but not other normal tissues.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Bispecific antibody A type of antibody that can bind to two different antigens at the same time. Bispecific antibodies are being studied in the imaging and treatment of cancer. They are made in the laboratory.

BRCA1/2 Genes that produce proteins that are involved in repairing damaged DNA. Females who inherit certain mutations in a *BRCA1* or *BRCA2* gene are at increased risk of developing breast cancer, ovarian cancer, and some other types of cancer. Males who inherit certain *BRCA1* or *BRCA2* mutations are at increased risk of developing breast cancer, prostate cancer, and some other types of cancer.

Breast cancer Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

Cachexia Loss of body weight and muscle mass, and weakness that may occur in patients with cancer, AIDS, or other chronic diseases.

Cancer A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinomas begin in the skin or in tissues that line or cover internal organs. Sarcomas begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemias arise in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the blood. Lymphomas and multiple myeloma originate in the cells of the immune system. Central nervous system cancers arise in the tissues of the brain and spinal cord. Also called malignancy.

Carcinogen Any substance that causes cancer.

Carcinoma A cancer that begins in the skin or in tissues that line or cover internal organs.

Caregiver A person who gives care to people who need help taking care of themselves. Examples include children, the elderly, or patients who have chronic illnesses or are disabled. Caregivers may be health professionals, family members, friends, social workers, or members of the clergy. They may give care at home or in a hospital or other health care setting.

Centers for Disease Control and Prevention (CDC) A federal agency, within the US Public Health Service of the Department of Health and Human Services, whose mission is to protect public health by preventing and controlling disease, injury, and disability. The CDC promotes healthy behaviors and safe, healthy environments. It keeps track of health trends, tries to find the cause of health problems and outbreaks of disease, and responds to new public health threats.

Cervical cancer Cancer that arises in the cervix (the area where the uterus connects to the vagina). The two main types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are caused by persistent infection with certain strains of human papillomavirus (HPV). Normal cells of the cervix do not suddenly become cancerous; they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

Chemotherapy The use of chemical substances to kill or slow the growth of cancer cells.

Chimeric antigen receptor (CAR) A receptor created in the laboratory that is designed to bind to certain proteins on cancer cells. It is then added to immune cells called T cells taken from cancer patients. This helps the T cells find and kill cancer cells that have a specific protein that the CAR is designed to bind to.

Chromosome Structure within the nucleus of a cell that contains genetic information (DNA) and its associated proteins. Except for sperm and eggs, nearly all nondiseased human cells contain 46 chromosomes.

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) A slow-growing cancer in which immature lymphocytes (white blood cells) are found in the blood and bone marrow and/or in the lymph nodes. CLL and SLL are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow. In SLL cancer cells are found mostly in the lymph nodes. CLL/SLL is a type of non-Hodgkin lymphoma.

Chronic myelogenous leukemia (CML) A slow-growing cancer in which too many myeloblasts—a type of immature blood cell that makes white blood cells called myeloid cells—are found in the blood and bone marrow. CML is usually marked by a chromosome change called the Philadelphia chromosome, in which a piece of chromosome 9 and a piece of chromosome 22 break off and trade places with each other. Also called chronic granulocytic leukemia and chronic myeloid leukemia.

Circulatory system The system that contains the heart and the blood vessels and moves blood throughout the body. This system helps tissues get enough oxygen and nutrients, and it helps them get rid of waste products. The lymph system, which connects with the blood system, is often considered part of the circulatory system.

Clinical trial A type of research study that tests how well new medical approaches work in people. These studies test new methods for screening, preventing, diagnosing, or treating a disease. Also called clinical study.

Clustered regularly interspaced short palindromic repeats (CRISPR) A laboratory tool used to change or "edit" pieces of a cell's DNA. CRISPR-based tools use specially designed RNA molecules to guide enzymes to a specific sequence of DNA. These enzymes then cut the strands of DNA at that point and may remove a small piece, causing a gap in the DNA where a new piece of DNA can be added. CRISPR-based tools are a breakthrough in science that will have important uses in many kinds of research. In cancer research, they may help to understand how cancer forms and responds to treatment as well as new ways to diagnose, treat, and prevent it.

Colonoscopy Examination of the inside of the colon using a colonoscope that is inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Colorectal cancer Cancer that forms in the colon or the rectum. More than 95 percent of colorectal cancers are adenocarcinomas that arise in cells forming glands that make mucus to lubricate the inside of the colon and rectum. Before a colorectal cancer develops, a growth of tissue or tumor usually begins as a noncancerous polyp on the inner lining of the colon or rectum. Polyps can be found—for example, through colonoscopy—and removed before they turn into cancer.

Computed tomography (CT) A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an X-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

COVID-19 A highly contagious respiratory disease that is caused by the SARS-CoV-2 virus.

Cytokine A type of protein that is made by certain immune and non-immune cells and has an effect on the immune system. Some cytokines stimulate the immune system and others slow it down.

Cytokine release syndrome (CRS) A condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR-T cells. Cytokine release syndrome is caused by a large, rapid release of cytokines into the blood from immune cells affected by the immunotherapy.

Cytotoxic An agent or substance that is toxic to living cells.

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) A protein found on T cells (a type of immune cell) that helps keep the body's immune responses in check. When CTLA-4 is bound to another protein called B7, it helps keep T cells from killing other cells, including cancer cells. Some anticancer drugs, called immune checkpoint inhibitors, are used to block CTLA-4. When this protein is blocked, the "brakes" on the immune system are released and the ability of T cells to kill cancer cells is increased.

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deep learning (DL) A type of machine learning that learns from huge amounts of data using complex algorithms, called artificial neural networks, that are modeled after how the human brain processes information.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

Diabetes A disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in elevated levels of glucose in the blood and urine.

Disability-adjusted life-years (DALYs) The measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death.

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

Endocrine therapy Treatment that adds, blocks, or removes hormones. For certain conditions (such as diabetes or menopause), hormones are given to adjust low hormone levels. Hormones can also cause certain cancers (such as prostate and breast cancer) to grow. To slow or stop the growth of cancer, synthetic hormones or other drugs may be given to block the body's natural hormones, or surgery is used to remove the gland that makes a certain hormone.

Epidermal growth factor receptor (EGFR) A protein found on the surface of some cells to which epidermal growth factor binds, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including many types of lung cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called ErbB1 and HER1.

Epigenetic modification A chemical change of DNA and/or histones that can control the accessibility of genes. The collection of epigenetic changes across the entire genome is referred to as the epigenome.

Epigenetics The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Extrachromosomal DNA (ecDNA) A double stranded DNA molecule found in various organisms, including humans, that is separate from chromosomes and can be located either inside or outside the nucleus of a cell. ecDNA can play roles in certain diseases including cancer.

Financial toxicity A term used to describe financial problems a patient has related to the cost of cancer care.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

Food and Drug Administration (FDA) An agency in the US federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. The FDA also makes sure that drugs, medical devices, and equipment are safe and effective, and that blood for transfusions and transplant tissue are safe.

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA and most genes contain the information for making a specific protein.

Genetic testing A laboratory method that looks for changes in genes, gene expression, or chromosomes in cells or tissue of a person. These changes may be a sign of a disease or condition, such as cancer. They may also be a sign that a person has an increased risk of developing a specific disease or condition or of having a child or other family member with the disease or condition. Genetic testing may also be done on tumor tissue to help diagnose cancer, plan treatment, or find out how well treatment is working.

Germline mutation A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Also called germline variant.

Glioblastoma multiforme (GBM) A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord.

Glioma A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

Health-related quality of life An individual's or a group's perceived physical and mental health over time.

HER2 A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ERBB2 and NEU.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma (HL) A cancer of the immune system that starts in white blood cells called lymphocytes.

Hormone One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human development index (HDI) A summary measure of average achievement in key dimensions of human development including lifespan, health span, knowledge accumulation, and having a quality standard of living.

Human immunodeficiency virus (HIV) The cause of acquired immunodeficiency syndrome (AIDS).

Human papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also plays a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

Immune checkpoint inhibitor (ICI) Type of immunotherapy that blocks immune checkpoint proteins from binding with partner proteins, which allow the body to recognize cancer cells.

Immune system A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from invading microorganisms and other foreign substances, destroys infected and malignant cells, and removes cellular debris. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines.

Immunotherapy Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, such as cancer.

Incidence rate The number of new cases per population at risk in a given time period.

Inflammation A normal part of the body's response to injury or infection. Inflammation occurs when the body releases chemicals that trigger an immune response to fight off infection or heal damaged tissue. Once the injury or infection is healed, the inflammatory process ends.

Large language model (LLM) A type of generative artificial intelligence trained on massive text datasets to understand and generate human-like language.

Late effects A health problem that occurs months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment and may include physical, mental, and social problems.

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Low-dose computed tomography (LDCT) A procedure that uses a computer linked to an x-ray machine that gives off a very low dose of radiation to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3D views of tissues and organs.

Lymph nodes See Lymphatic system.

Lymphatic system The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen,

thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body. Also called lymph system.

Lymphocyte-activation gene 3 (LAG-3) A cell surface molecule with diverse biologic effects on T cell function. LAG-3 binds to proteins known as MHC class II and negatively regulates proliferation, activation and homeostasis of T cells, in a similar fashion to PD-1.

Lymphoma Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells.

Lynch syndrome An inherited disorder that increases the risk of developing colorectal cancer, endometrial cancer, ovarian cancer, and many other types of cancer, such as cancers of the stomach, small intestine, pancreas, bile duct, urinary tract, and brain, often before age 50. Lynch syndrome is caused by mutations (changes) in genes that affect DNA mismatch repair, a process that fixes mistakes that occur when DNA is copied. These genes are *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*.

Machine learning (ML) A field of computer science that develops the processes by which computers are taught how to learn and perform certain functions without being specifically programmed to perform those functions. Machine learning involves analyzing very large amounts of information to improve a computer's ability to make decisions or predictions. Machine learning is a part of artificial intelligence (AI). In medicine, the use of machine learning and AI may help improve cancer screening and diagnosis and plan treatment.

Magnetic resonance imaging (MRI) A noninvasive medical test that produces detailed pictures of areas inside the body through the use of radio waves and a powerful magnet linked to a computer. MRI is particularly useful for imaging the brain, spine, soft tissue of joints, and inside of bones. Also called nuclear magnetic resonance imaging (NMRI).

Mammogram An X-ray of the breast that is used to look for early signs of breast cancer.

Melanoma Cancer that begins in melanocytes (cells that make the pigment melanin). These cancers may arise in a mole (skin melanoma), but they can also originate in other pigmented tissues, such as the eye (uveal melanoma) or the intestines (mucosal melanoma).

Metastasis The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

Microbiome Describes the community of organisms (fungi, bacteria, and virus) that exists in a particular environment, such as a part of the body including the skin, gastrointestinal tract, or tumor.

Molecularly targeted therapy A type of treatment that uses therapeutics to target specific molecules involved in the growth and spread of cancer cells.

Morbidity Refers to having a disease, a symptom of disease, the amount of disease within a population, or the medical problems caused by a treatment.

Multi-cancer early detection (MCED) A type of blood test that is being studied as a way to screen for many types of cancer at the same time. These tests work by measuring biomarkers, such as pieces of DNA, that cancer cells release into the blood as they die. They may help find cancer in parts of the body that are not easily accessible for physical exam or biopsy. MCED tests may be used with other screening tests to help find more cancers before they cause symptoms. MCED tests are a type of liquid biopsy.

Multi-omics Data that integrate multiple layers of biological information—for example, proteogenomics combines genomic, transcriptomic, and proteomic data to link DNA and RNA alterations to protein expression—to provide a comprehensive view of the molecular changes underpinning cancer biology.

Multiple myeloma (MM) A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

Mutagen Anything that causes a mutation (a change in the DNA of a cell). DNA changes caused by mutagens may harm cells and cause certain diseases, such as cancer. Examples of mutagens include radioactive substances, X-rays, ultraviolet radiation, and certain chemicals.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

Myeloma Cancer that arises in plasma cells, a type of white blood cell.

National Cancer Institute (NCI) The largest of the 27 institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

National Institutes of Health (NIH) A federal agency in the US that conducts biomedical research in its own laboratories; supports the research of non-federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of research investigators; and fosters communication of medical information.

Neoadjuvant therapy Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

Neoantigen A new protein that forms on cancer cells when certain mutations occur in tumor DNA. Neoantigens may play an important role in helping the body make an immune response against cancer cells. Neoantigens used in vaccines and other types of immunotherapy are being studied in the treatment of many types of cancer.

Nervous system The organized network of nerve tissue in the body. It includes the central nervous system (the brain and spinal cord), the peripheral nervous system (nerves that extend from the spinal cord to the rest of the body), and other nerve tissue.

Non-Hodgkin lymphoma (NHL) A term for a large group of cancers that arise in B cells or T cells. Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Cutaneous T-cell lymphoma is one example of a T-cell non-Hodgkin lymphoma.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

Oncogene A mutated gene that has the potential to cause cancer. Proto-oncogenes are oncogenes before they become mutated.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

Palliative care Care given to improve the quality of life and help reduce pain in people who have a serious or life-threatening disease, such as cancer. The goal of palliative care is to prevent or treat, as early as possible, the symptoms of the disease and the side effects caused by treatment of the disease. It also attends to the psychological, social, and spiritual problems caused by the disease or its treatment.

Pandemic An outbreak of a disease that occurs over a wide geographic area across international boundaries and affects an exceptionally high proportion of the population.

Pathogen A bacterium, virus, or other microorganism that can cause disease. Also called infectious agent.

Patient navigator A person who helps guide a patient through the health care system. This includes help going through the screening, diagnosis, treatment, and follow-up of a medical condition, such as cancer. A patient navigator helps patients communicate with their health care providers, so they get the information they need to make decisions about their health care. Patient navigators may also help patients set up appointments for doctor visits and medical tests and get financial, legal, and social support. They may also work with insurance companies, employers, case managers, lawyers, and others who may have an effect on a patient's health care needs. Also called patient advocate.

Patient reported outcome (PRO) Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

Peptide A molecule that contains two or more amino acids (the molecules that join together to form proteins). Peptides that contain many amino acids are called polypeptides or proteins.

Precision medicine In oncology, precision medicine refers to the tailoring of treatments to the individual characteristics—in particular, the genetics—of patients and their cancer.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells. When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD-1 acts as an immune checkpoint protein or brake.

Programmed death-ligand 1 (PD-L1) A protein on the surface of many cell types, including some tumor cells. When it attaches to PD-1 on the surface of T cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively.

Prostate cancer Cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the

bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Prostate-specific membrane antigen (PSMA) A protein that is usually found on the surface of normal prostate cells but is found in higher amounts on prostate cancer cells. PSMA may be used as a target in imaging to help find prostate cancer cells, especially those that may have come back or spread to other parts of the body.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Quality of life The overall enjoyment of life. In cancer care, the term refers to an individual's sense of well-being and ability to carry out activities of daily living.

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radionuclide An unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. In cancer medicine, radionuclides are used in diagnostic tests to detect the spread of cancer using imaging as well as in therapeutics, called radiopharmaceuticals, to treat cancer. Also called radioisotope

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Ribonucleic acid (RNA) RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins.

Sarcoma Type of cancer that begins in the bones and connective tissues such as muscle, fat, blood vessels, nerves, tendons, and the lining of joints.

Sarcopenia A condition characterized by loss of muscle mass, strength, and function in older adults. Older age, getting little or no exercise, and poor nutrition may increase the risk of sarcopenia. Sarcopenia may also occur in people with cancer.

Signaling pathway/signaling network A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it alters the activity of another molecule. This process is repeated until the last molecule is activated, and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help prevent cancer cell growth and kill cancer cells.

Social drivers of health (SDOH) The social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and grow older that can affect their health, well-being, and quality of life. These include economic policies and systems, development agendas, social norms, social policies, and political systems. Also called social determinants of health.

Sociodemographic index (SDI) A number from 0 to 1 that identifies where countries or geographic areas sit on the spectrum of development. It combines rankings of per capita income, average education attainment, and fertility rates.

Somatic mutation An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. Also known as acquired mutations.

Spatial transcriptomics A technique to count the number of transcripts of a gene at distinct spatial locations in a cell or tissue which can be used to assign cell types to specific locations within a sample.

Splicing Process that involves the removal or "splicing out" of certain sequences referred to as intervening sequences, or introns. The final mRNA consists of the remaining sequences, called exons, which are connected to one another through the splicing process.

Stepped-care A systematic approach to treating symptoms in cancer patients, including depression, pain, and fatigue by

starting with the least expensive, most simple method first and only increasing intervention when needed.

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Treatment resistance The failure of cancer cells to respond to a treatment used to kill or weaken them. The cells may be resistant at the beginning of treatment or may become resistant after being exposed to the treatment.

Triple-negative breast cancer (TNBC) A type of breast cancer in which the cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative, PR-negative, HER2-negative breast cancer.

Tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

Tumor heterogeneity A term that describes the differences between tumors of the same type in different patients, the differences between cancer cells within a single tumor, or the differences between a primary (original) tumor and a secondary tumor. These differences may involve the tumor's genes and proteins. For example, some cancer cells in a tumor may have genetic mutations (changes) that are not present in other cancer cells in that tumor. Tumor heterogeneity can play an important role in how cancer is diagnosed and treated and how it responds to treatment.

Tumor microenvironment The cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

Ultraviolet (UV) radiation Invisible rays that are part of the energy that comes from the sun. Ultraviolet radiation that reaches the Earth's surface is made up of two types of rays, called UVA and UVB. Ultraviolet radiation also comes from sun lamps and tanning beds. It can cause skin damage, premature aging, melanoma, and other types of skin cancer. It can also cause problems with the eyes and the immune system. Skin specialists recommend that people use sunscreens that protect the skin from both kinds of ultraviolet radiation. In medicine, ultraviolet radiation also comes from special lamps or a laser and is used to treat certain skin conditions such as psoriasis, vitiligo, and skin tumors of cutaneous T-cell lymphoma.

United States Preventive Services Task Force (USPSTF) Independent, volunteer panel of national experts in disease prevention and evidence-based medicine that makes evidence-based recommendations about clinical preventive services.

Vaccine A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

Wearable device Any device designed to be used while worn in close contact to the skin, and can detect, analyze, and transmit information to the wearer and other designated individuals.

Appendix

SUPPLEMENTARY TABLE 1

Carcinogenic Toxins Released by Wildfires

Wildland fire personnel—first responders trained to prevent, suppress, and manage wildfires—across the United States and globally work to address the accelerating wildfire activity. In combating wildfires, wildland fire personnel are exposed to multiple hazardous materials via smoke, dust, and ash. This table provides a list of chemicals that wildland personnel encounter as an occupation and the EPA classification of the exposure based on the weight of scientific evidence.

Chemical Class	Chemical	EPA Classification
PARTICULATE MATTER	PM10	-
	PM, respirable (≤4μm)	-
	PM, total	-
POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)	Benz[a]anthracene	B2
	Benzofluoranthenes	B2
	Benzo[b]fluoranthene	B2
	Benzo[j]fluoranthene	B2
	Benzo[k]fluoranthene	B2
	Benzo[c]phenanthrene	B2
	Benzo[a]pyrene	CH
	Chrysene	B2
	Cyclopenta[c,d]pyrene	-
	Dibenz[a,h]anthracene	B2
	Indeno[1,2,3-cd]pyrene	B2
	Naphthalene	C
	Pyrene, 1-hydroxypyrene (1-HP), surrogate for PAHs	D
METALS	Arsenic and inorganic arsenic compounds	A
	Beryllium and beryllium compounds	B1
	Cadmium and cadmium compounds	B1
	Chromium, metallic	A (via inhalation)
	Lead	B2
	Nickel compounds	A
VOLATILE ORGANIC COMPOUNDS (VOCs)	Acetaldehyde	B2
	Acrolein	-
	Benzene	CH
	Ethylbenzene	D
	Formaldehyde	B1
	Styrene	-
OTHER	Asbestos (all forms)	A
	Carbon black	-
	Radionuclides	-
	Silica dust (Quartz and Cristobalite)	-

Environmental Protection Agency's Weight of Evidence (EPA WOE) for carcinogenicity: A, human carcinogen, B1, probable carcinogen, limited human evidence; B2, probable carcinogen, sufficient evidence in animals; C, possible human carcinogen; CH, carcinogenic to humans; D, not classifiable; not listed, not evaluated or included in EPA's WOE for carcinogenicity; PM≥10, fine and coarse particulate matter. These particles vary in size and can consist of hundreds of different chemicals. However, only those that are 10 micrometers or smaller are regulated by the EPA, as they can penetrate deep into the lungs and even can be absorbed into the bloodstream.

Sources: (177,335).

SUPPLEMENTARY TABLE 2

Surgeries for the Prevention of Cancer

Genetic Mutation	Cancer	Technique	Removes
APC	Colon cancer	Colectomy	Colon/large intestine
BRCA1 or *BRCA2*	Breast and ovarian cancers	Mastectomy and salpingo-oophorectomy	Breasts, and ovaries and fallopian tubes
CDKN2A, *STK11*, *BRCA2*-positive family history	Pancreatic cancer	Pancreatectomy	Complete pancreas
CDKN2A, *CDK4*, and other genes associated with familial melanoma and dysplastic nevus syndrome	Melanoma	Excision	High-risk moles
CDH1	Breast and stomach cancers	Mastectomy and gastrectomy	Breast and stomach
Mutations associated with Lynch syndrome	Colon, endometrial, and ovarian cancers	Colectomy, hysterectomy, and salpingo-oophorectomy	Colon/large intestine, uterus, and ovaries and fallopian tubes
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

SUPPLEMENTARY TABLE 3

Newly FDA-approved Anticancer Agents (July 1, 2024–June 30, 2025)

Type of Treatment	Generic Name	Trade Name	What It Is	Approved For	Clinical Trial(s)	Administered As
MOLECULARLY TARGETED THERAPY	▶ avutometinib + defactinib	Avmapki + Fakzynja	Cell-signaling inhibitor	Certain type of ovarian cancer	NCT04625270	Tablet/Capsule
	belzutifan	Welireg	Gene transcription modifier	Pheochromocytoma or paraganglioma†	NCT04924075	Tablet/Capsule
	cabozantinib	Cabometyx	Angiogenesis inhibitor	Certain types of pancreatic and extra-pancreatic neuroendocrine tumors†	NCT03375320	Tablet/Capsule
	▶ datopotamab deruxtecan-dlnk	Datroway	Cell-signaling inhibitor	Certain types of breast and lung cancers	NCT04484142 NCT04656652	Injection
	▶ denileukin diftitox-cxdl	Lymphir	Cell-lysis mediator	Certain type of lymphoma	NCT01871727	Injection
	▶ ensartinib	Ensacove	Cell-signaling inhibitor	Certain type of lung cancer	NCT02767804	Tablet/Capsule
	▶ inavolisib* + palbociclib + fulvestrant	Itovebi	Cell-signaling inhibitor	Certain type of breast cancer	NCT04191499	Tablet/Capsule + Injection
	▶ lazertinib + amivantamab-vmjw	Lazcluze + Rybrevant	Cell-signaling inhibitor	Certain type of lung cancer	NCT04487080	Tablet/Capsule + Injection
	▶ mirdametinib	Gomekli	Cell-signaling inhibitor	Plexiform neurofibromas	NCT03962543	Tablet/Capsule
	▶ revumenib	Revuforj	Gene transcription modifier	Certain types of leukemia	NCT04065399	Tablet/Capsule
	sotorasib* + panitumumab	Lumakras + Vectibix	Cell-signaling inhibitor	Certain type of colorectal cancer†	NCT05198934	Tablet/Capsule + Injection
	▶ taletrectinib	Ibtrozi	Cell-signaling inhibitor	Certain type of lung cancer	NCT04395677 NCT04919811	Tablet/Capsule
	▶ telisotuzumab vedotin-tllv*	Emrelis	Cell-signaling inhibitor	Certain type of lung cancer	NCT03539536	Injection
	▶ vimseltinib	Romvimza	Cell-signaling inhibitor	Tenosynovial giant cell tumor	NCT05059262	Tablet/Capsule
	▶ vorasidenib	Voranigo	Epigenome-modifying agent	Certain types of brain tumor	NCT04164901	Tablet/Capsule
	▶ zanidatamab-hrii*	Ziihera	Cell-signaling inhibitor	Biliary tract cancer	NCT04466891	Injection
	▶ zenocutuzumab-zbco	Bizengri	Cell-signaling inhibitor	Certain types of lung and pancreatic cancers	NCT02912949	Injection
IMMUNOTHERAPY	▶ afamitresgene autoleucel	Tecelra	TCR T-cell therapy	Synovial sarcoma	NCT04044768	Injection
	▶ cosibelimab-ipdl	Unloxcyt	Immune checkpoint inhibitor	Cutaneous squamous cell carcinoma	NCT03212404	Injection
	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of bladder cancer†	NCT03703297	Injection
	▶ obecabtagene autoleucel	Aucatzyl	CAR T-cell therapy	Certain type of leukemia	NCT04404660	Injection
	pembrolizumab	Keytruda	Immune checkpoint inhibitor	Pleural mesothelioma†	NCT02784171	Injection
	▶ penpulimab-kcqx	–	Immune checkpoint inhibitor	Nasopharyngeal carcinoma	NCT04974398	Injection
	retifanlimab-dlwr	Zynyz	Immune checkpoint inhibitor	Certain type of anal cancer†	NCT04472429	Injection
	tafasitamab-cxix	Monjuvi	Cell-lysis mediator	Certain type of lymphoma†	NCT04680052	Injection
	▶ zolbetuximab-clzb*	Vyloy	Cell-lysis mediator	Gastric or gastroesophageal junction cancers	NCT03504397 NCT03653507	Injection
DEVICE	Optune Lua		Tumor treating fields device	Certain type of lung cancer†	NCT02973789	—

▶ Denotes newly approved anticancer agents.

CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; TCR, T-cell receptor.

* Approved with a new companion diagnostic test.

† Expanded approval for use in new cancer type.

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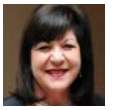

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Mission

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 membership includes more than 58,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 141 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.
- With AACR-Minorities in Cancer Research and AACR-Women in Cancer Research, AACR supports the professional development and career advancement of underrepresented minority and women scientists in cancer research.
- Open to any AACR member are Scientific Working Groups to explore expanded research opportunities and advance discoveries that lead to greater knowledge and understanding of cancer.

Publications

- With 10 prestigious publications that collectively cover basic cancer biology, translational efforts, clinical investigation, epidemiology, and prevention, the journals of the AACR are trusted channels for rigorously vetted discoveries spanning from bench to bedside.
- *Cancer Today*® is a magazine for cancer patients and caregivers.
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- The AACR Cancer Progress Reports are a cornerstone of AACR's educational and advocacy efforts. The purpose of these reports 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 funds research directly, as well as in collaboration 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 awarded over $542 million in funding for cancer research projects.

Meetings

AACR hosts more than 30 scientific conferences and educational workshops annually. The largest of these events is the AACR Annual Meeting. The next AACR Annual Meeting will be held April 17–22, 2026, in San Diego, California.

Policy and Advocacy

- The AACR Office of Science Policy and Government Affairs actively communicates with legislators and policymakers about the value of cancer research and related biomedical sciences to reduce cancer-related morbidity and mortality. It also advocates for critical federal cancer research funding.
- The AACR Scientist↔Survivor Program® provides support for cancer survivors and their families.

AACR Project GENIE®

AACR Project GENIE® is an open access, international, pancancer registry of real-world clinico-genomic data assembled through data sharing between a consortium 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

The AACR Foundation is the philanthropic arm of the AACR. Funds raised by the AACR Foundation from individuals, foundations, corporate partners, and others provide vital support for the AACR's groundbreaking programs and initiatives—helping advance the AACR's mission to prevent and cure all forms of cancer.

Professional Development

AACR supports education and training of cancer scientists and clinicians and provides professional development opportunities and resources to enhance and advance their careers. AACR CancerCareers.org is one resource that offers unparalleled career services and opportunities to cancer biomedical researchers and to potential employers who seek to recruit them.

American Association for Cancer Research®

FINDING CURES TOGETHER®

The mission of the American Association for Cancer Research (AACR) is to prevent and cure all cancers through research, education, communication, collaboration, science policy and advocacy, and funding for cancer research.

Through its programs and services, the AACR fosters cutting edge research in cancer and related sciences; accelerates the dissemination of new research findings among scientists, clinicians, patient advocates, and others dedicated to preventing and curing all cancers; promotes science education and training; and advances the understanding of cancer etiology, prevention, detection, diagnosis, regulatory science, and treatment throughout the world.

As the leading scientific organization dedicated to the conquest of all cancers and to the core values of diversity, equity, and inclusion, the AACR works to eliminate cancer health disparities through scientific and policy initiatives, and to eradicate racism and racial inequality in cancer research. The AACR is deeply committed to realizing the bold vision of health equity for all populations.

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