Spotlight on
CANCER IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

AACR American Association for Cancer Research®

CANCER PROGRESS REPORT

2024

Inspiring Science.
Fueling Progress.
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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 142 countries and territories around the world. Presently, 32% of members live outside the United States and 22% of AACR's international members are located in countries with emerging economies. 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

We are living in a transformative era for cancer research. In the United States, the overall cancer death rate is declining steadily, and the number of cancer survivors has reached an unprecedented level. This remarkable progress is driven by breakthroughs across all areas of cancer science and medicine, even tackling once intractable diseases such as advanced lung cancer and metastatic melanoma. Fueled by trailblazing scientific discoveries and technological innovations, we are now positioned to achieve even greater advances that will save countless more lives.

The *AACR Cancer Progress Report 2024* highlights the significant strides made possible through medical research, much of which is supported by federal investments in the National Institutes of Health (NIH), National Cancer Institute (NCI), US Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC). These investments have catalyzed a wave of scientific breakthroughs that are deepening our understanding of the biological complexities of cancer and accelerating the development of more effective tools for prevention, detection, diagnosis, and treatment.

Noteworthy advancements between July 1, 2023, and June 30, 2024, the 12 months covered in this report, include the approval by FDA of 15 new anticancer therapeutics and the expansion of 15 previously approved therapeutics for the treatment of additional cancer types. During the same period, FDA also approved a new imaging agent to aid breast cancer surgery, several artificial intelligence (AI)-based tools to improve early detection and diagnosis of cancers, and two minimally invasive tests for assessing inherited cancer risk or for early detection of cancer.

Among the newly approved treatments highlighted in this report are the first tumor-infiltrating lymphocyte therapy, a pioneering immunotherapy strategy, for advanced melanoma; a new bispecific antibody against a novel target for patients with small cell lung cancer, a particularly intractable disease; and several new molecularly targeted therapeutics and immunotherapeutics for the treatment of an array of blood cancers. Advances in personalized treatment for cancers driven by mutated KRAS, one of the most frequently altered genes in cancer and long assumed to be "undruggable," continue unabated with the approval of a KRAS-targeted therapeutic to treat colorectal cancer.

Spectacular progress has also been made against childhood cancers, with groundbreaking clinical advances that are transforming outcomes for patients. While cancer remains the leading cause of death by a disease among children, the landscape of childhood cancer care is evolving rapidly, driven by innovative research, new treatments, and a deeper understanding of the unique biology of childhood cancers. Just in the 12 months covered in this report, FDA approved three molecularly targeted therapeutics for the treatment of common childhood cancers, such as glioma and neuroblastoma, as well as exceedingly rare pediatric cancers driven by alteration in the NTRK gene.

Despite these achievements, in 2024, it is estimated that more than two million new cases of cancer will be diagnosed in the United States and more than 611,000 people will die from the disease. Globally, there were an estimated 20 million new cancer cases and over 9.7 million deaths from cancer in 2022. Unfortunately, cancer continues to present numerous complex challenges. Incidence rates for some cancers are increasing. Of particular concern among public health experts are the rising cases of breast, colorectal, gastric, and certain blood cancers in adults younger than 50, reasons for which are not fully understood. Additionally, as we detail in the recently published AACR Cancer Disparities Progress Report 2024, health inequities persist, with racial and ethnic minorities and other medically underserved populations bearing a disproportionate burden of cancer.

Looking to the future, we strongly believe that we have never been in a better position to bring lifesaving cancer science from the laboratory to the clinic. Integration of emerging technologies, such as sophisticated tumor profiling, liquid biopsies, AI, and novel drug delivery systems, promises to open new frontiers in cancer medicine and revolutionize patient care. And while we continue to push the boundaries of science, our goal is clear: it aims to provide every cancer patient with the best possible chance for a cure and a long, healthy life, even those who have been diagnosed with metastatic disease.

The bipartisan support for NIH and NCI funding has been instrumental in our progress against cancer, and continued investment will ensure that we sustain this momentum. It is concerning that after almost a decade of growing federal budgets for medical research, Congress cut NIH funding in fiscal year (FY) 2024. This budget reduction threatens to curtail the progress seen in recent years and stymie future strides against cancer. Therefore, AACR urges Congress to uphold robust funding increases for these critical institutions, as well as for FDA and CDC, to drive forward the next wave of breakthroughs in cancer science and medicine.

Together, with sustained commitment and investment, we can continue to push the boundaries of what is possible in cancer research and patient care and move closer to the goal of preventing and curing all cancers for all populations.

Patricia M. LoRusso, DO, PhD (hc), FAACR
President, AACR

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

Executive Summary

We are witnessing tremendous progress against the collection of diseases we call cancer. The rapid pace of these advances is attributable to research discoveries in basic, translational, clinical, and population science as well as technological innovations that are continually being translated to improvements in cancer prevention, detection, diagnosis, and treatment.

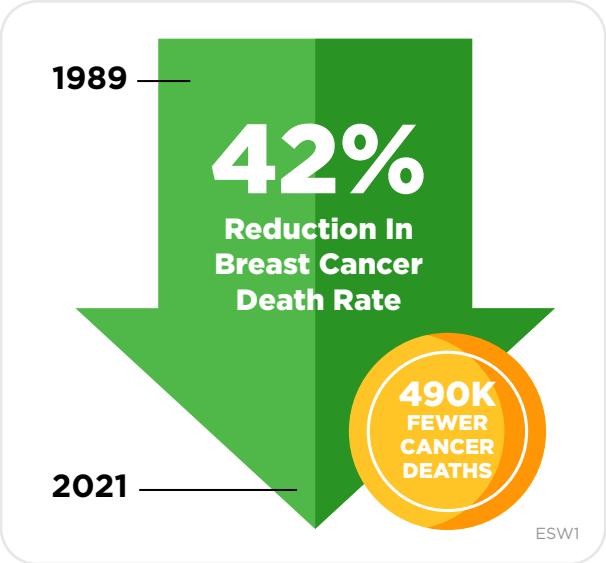
As the first and largest professional organization in the world whose mission is to prevent and cure all cancers, the American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the importance of medical research for saving lives. It is also committed to advocating for increased federal funding to government entities that fuel progress against cancer, in particular, the National Institutes of Health (NIH), National Cancer Institute (NCI), United States (US) Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC).

The annual AACR Cancer Progress Report to Congress and the American public is a cornerstone of AACR's educational and advocacy efforts. This fourteenth edition of the report highlights how medical research continues to extend and improve lives, like the lives of the courageous individuals featured in this report who have shared their experiences with cancer. It also underscores how federal funding for NIH, NCI, FDA, and CDC is vital if we are to maintain the momentum of progress against cancer for the benefit of all patients.

Cancer in 2024

The spectacular progress being made against cancer is resulting in a steady decline in cancer death rates, and a consistent rise in the number of people who live longer and fuller lives after a cancer diagnosis. In fact, the overall cancer death rate in the United States has fallen by 33 percent between 1991 and 2021, a reduction that translates into averting more than 4.1 million deaths from cancer. The drop in overall cancer mortality is attributable to reductions in smoking, as well as improvements in early detection and treatment of certain cancers.

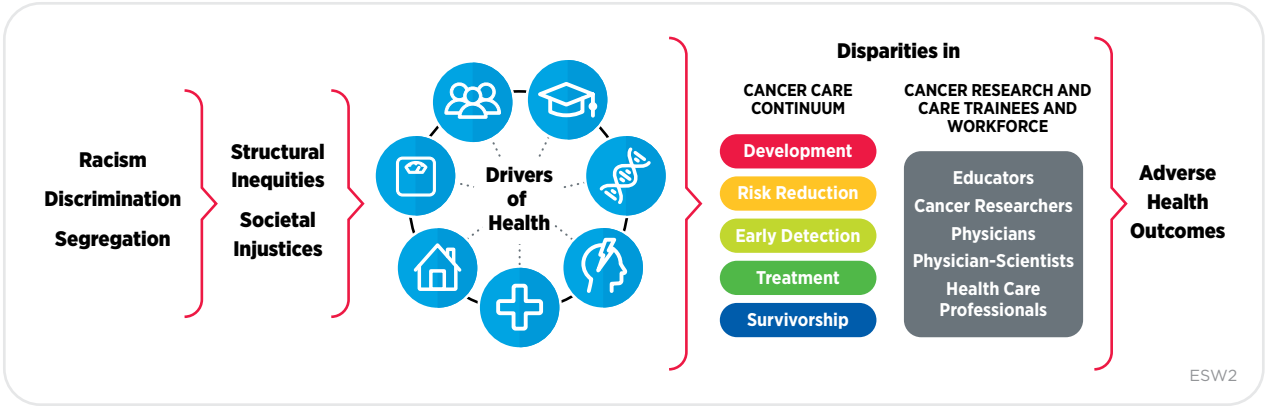
The steady decline in death rates for colorectal cancer and female breast cancer since the 1990s has helped drive down overall US cancer mortality. In addition, the decrease in US lung cancer death rate, the pace of which has accelerated in recent years, has contributed significantly to reducing the overall US cancer death rate in the past decade. Further contributing to the progress are the downward trends in death rates for leukemia, melanoma, and kidney cancer, attributable to breakthroughs in precision medicine.



Thanks to the research-driven advances, more than 18 million individuals with a history of cancer were alive in the United States as of January 1, 2022, and the number is projected to rise to 26 million by 2040.

Even though significant progress has been made, cancer continues to be an ongoing public health challenge in the United States and around the world. In the United States alone, it is estimated that more than two million new cancer cases will be diagnosed in 2024. Among the challenges we face is that the advances have not been uniform for all types and stages of cancer. As one example, while the overall cancer incidence in the United States has stabilized in recent years, cases of certain cancer types, such as pancreatic cancer, uterine cancer, and human papillomavirus (HPV)-associated oral cancers, are increasing. Furthermore, the age- and sex-specific incidence of certain cancers is on the rise. For instance, a growing concern among public health experts is the rising incidence of early-onset colorectal cancer—cancer in adults younger than 50 years.

Another significant challenge we face is the disproportionately higher burden of cancer in US racial and ethnic minority groups and other medically underserved populations. Cancer disparities are driven largely by complex and interrelated structural and social factors. Increased collaboration among all stakeholders working toward the bold vision of health equity is vital if we are to ensure that research-driven advances against cancer benefit all patients, regardless of their race, ethnicity, age, sexual orientation, gender identity, socioeconomic status, or geographic location.



The burden of cancer and its economic toll, both on individuals and on the US health care system, 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 and the support from the federal government. Importantly, public sector funding from NIH and NCI directly benefits patients through the development of lifesaving anticancer therapeutics and preventive interventions. Continued federal investments in NIH, NCI, FDA, and CDC will help the medical research community maintain the momentum of scientific and technological innovation and ensure that we meet the President's goal of reducing US cancer death rates by half by 2047.

★ SPOTLIGHT

The Landscape of Childhood, Adolescent and Young Adult (AYA) Cancers

This edition of the AACR Cancer Progress Report highlights the state of cancer in children and AYAs across the cancer continuum. A dedicated spotlight is included in all the relevant sections throughout the report.

Cancers are rare in children (14 years and younger), adolescents (15 to 19 years), and young adults (20 to 39 years). In the United States in 2024, approximately 9,620 children and 5,290 adolescents will be diagnosed with cancer. Leukemia and cancers of the nervous system, including brain tumors, are the most common cancers in children. Among adolescents, brain and nervous system tumors are the leading causes of new cancer cases, followed by lymphoma and leukemia.

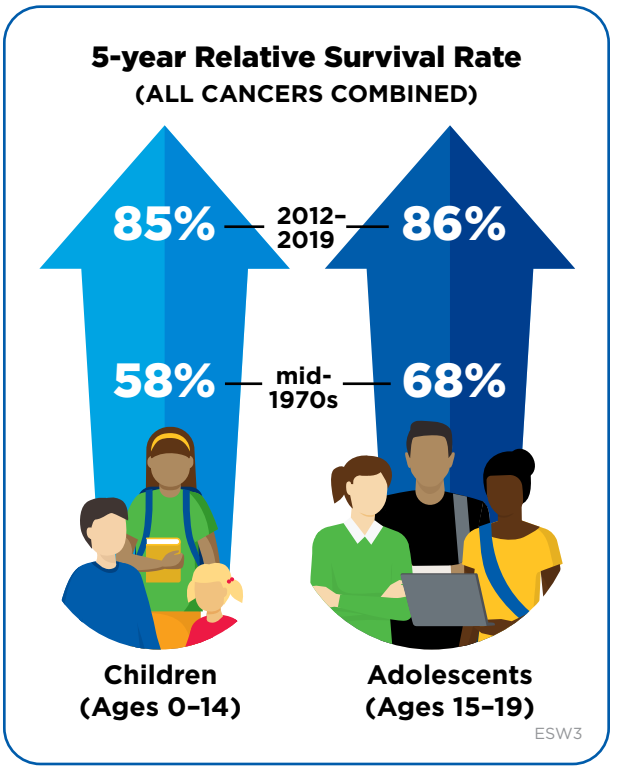
In contrast, young adults are most commonly diagnosed with solid tumors, including thyroid cancer, melanoma, and breast cancer.

Research over the past two decades has uncovered key biological differences between childhood and adult cancers. For example, emerging evidence indicates that genetic mutations inherited from parents play an important role in the development of childhood cancers. Another difference is the greater prevalence of structural DNA alterations, such as chromosomal rearrangements, in childhood cancers. Recent findings have identified nearly 300 fusion genes arising from chromosomal rearrangements that are associated with childhood cancers.

The knowledge that inherited genetic mutations play an important role in the development of childhood cancers is also helping researchers to develop surveillance strategies for monitoring and managing the risk of childhood cancers. For example, researchers have developed specific genetic tests, as well as surveillance recommendations, to monitor children who have Li–Fraumeni syndrome, a collection of diseases that is caused by inherited mutations in the *TP53* gene and predisposes children to a wide range of early-onset cancers, including soft tissue sarcomas, osteosarcomas, breast cancer, brain tumors, and leukemia.

Modifiable risk factors play a far less critical role in the development of childhood cancers compared to cancers in adults. Regardless, there is some evidence that exposure to certain modifiable factors can increase the risk of cancer among children. AYA individuals diagnosed with cancer can be exposed to similar modifiable cancer risk factors as adults, and for a greater length of time compared to children. When combined with genetic predispositions, e.g., Lynch syndrome, such exposures can further increase the risk of cancer development.

According to NCI, an estimated 84,100 AYA individuals will be diagnosed with cancer in the United States in 2024, which is 4.2 percent of all cancer diagnoses. Although this is a small percentage compared to adults



who receive a diagnosis of cancer, there has been a rise in certain types of early-onset cancers that are caused by a combination of factors including genetic predisposition, diet, microbiome, excess body weight, and environmental exposures. Infection with certain pathogens can also increase the risk of cancer in this group.

The unprecedented progress in the treatment of childhood and AYA cancers is reflected in the greater than 85 percent 5-year relative survival rates for all cancers combined among childhood and AYA patients. Many of the initial advances in the treatment of childhood cancers were made through intensification of cytotoxic chemotherapeutics, which while effective were associated with significant toxicities, including late and long-term adverse effects. With greater understanding of the biology of childhood and AYA cancers and innovations in technology, there is an increasing focus on utilizing personalized approaches to target cancers more precisely as well as on reducing treatment intensities among patients who have a favorable prognosis, to improve their quality of life. The National Cancer Institute is leading the efforts to harness the knowledge gleaned from genomic analyses of childhood cancers to develop strategies for precision or personalized medicine. In recent years, FDA has approved a broad array of precision therapeutics to treat a variety of childhood cancers.

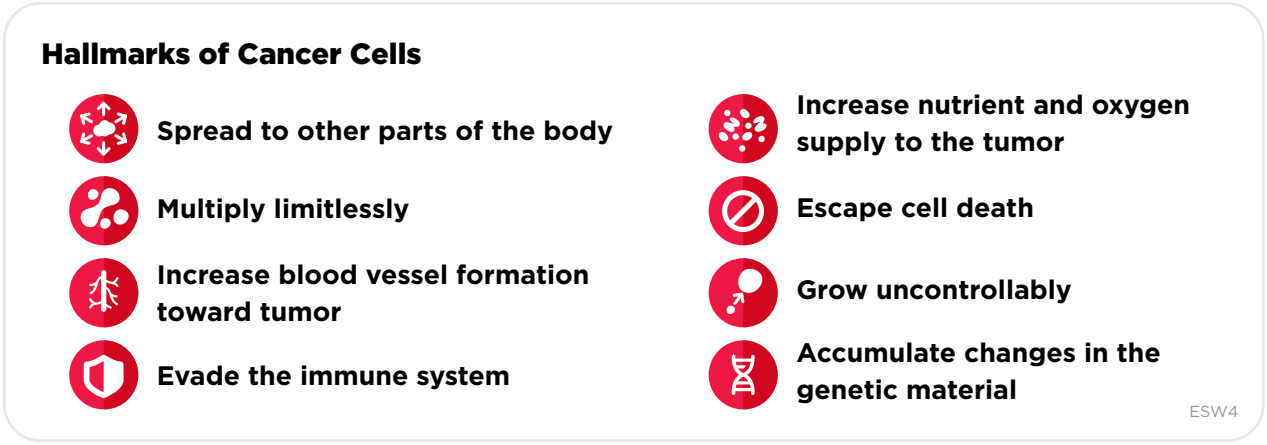
Just in the 12 months covered by this report (July 1, 2023–June 30, 2024), FDA approved a new molecularly targeted therapy, tovorafenib (Ojemda), for the treatment of children with certain brain tumor types. During the same period, FDA also expanded the use of a molecularly targeted therapeutic, eflornithine (Iwilfin), previously approved for certain infectious and hormonal diseases, as the first treatment to reduce the risk of relapse in children with high-risk neuroblastoma. In addition, FDA expanded the use of a molecularly targeted therapeutic, repotrectinib (Augtyro) previously approved for patients with certain type of lung cancer for the treatment of children with any solid tumor that has certain genetic alterations. Furthermore, several molecularly targeted therapeutics and immunotherapeutics that were already approved by FDA for use in adults with certain cancers received expanded approvals for the treatment of children with the same types of cancer. The promise of these therapeutics is illustrated through the personal experiences of **Michael Methner** (see p. 125) and **Parker Shaw** (see p. 127).

Despite major progress, some cancers in children and AYA, such as sarcomas or certain brain tumors, have been difficult to treat and continue to have poor survival. Childhood and AYA cancer survivors such as **Lourdes Monje** (see p. 137) also face unique challenges compared to their peers who have never been diagnosed with cancer. These challenges include long and late-term side effects from cancer and its treatments, financial toxicity, difficulty finding work, lower levels of educational attainment, psychosocial issues, and others. Because of the unique challenges faced by this population, researchers and care providers must ensure that the needs of this population are adequately addressed across the spectrum of cancer care.

Understanding the Path to Cancer Development

Seminal contributions from decades of research in basic, clinical, translational, and population science have established cancer as a collection of diseases that are characterized by uncontrolled cell division. A key insight from this knowledge is that different cancer types share many 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.

Research has shown that hallmarks of cancer are primarily acquired through mutations in the genetic material of normal cells. There are two types of genetic mutations associated with



cancer: inherited and somatic. Inherited mutations are passed on 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 from errors made during cell division, or due to exposure to modifiable risk factors including smoking, certain viral infections, and UV radiation and/or cancer-causing chemicals.

Cancer initiation, development, and progression are all multistep processes that are further influenced by changes inside and outside the cell. As the disease progresses, cancer cells acquire additional characteristics that enable them to establish mutually beneficial interactions with their surroundings, known as the tumor microenvironment. Research has shown that the tumor microenvironment affects the growth of cancer cells and cancer cells influence the tumor microenvironment to promote their survival.

Technological advances in understanding cancer at the levels of single cells and molecules have demonstrated that each patient's cancer is unique. This important 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 anticancer therapeutics to treat cancer types for which there were no effective treatment options just two decades ago.

Reducing the Risk of Cancer Development

Research in basic, translational, and population sciences has broadened our understanding of the factors that increase an individual's risk of developing cancer. It is estimated that 40 percent of all cancer cases in the United States are attributable to preventable causes. Many of these risk factors are modifiable, such as reducing tobacco use, avoiding an unhealthy diet, staying physically active, limiting exposure to UV radiation, reducing or eliminating alcohol consumption, and preventing and treating cancer-causing pathogenic infections.

Between 1991 and 2021 the overall cancer mortality in the United States declined by 33 percent, in part due to the implementation of public health campaigns and policy initiatives that helped reduce smoking and increase early detection of cancers. Although smoking rates have declined, the increasing prevalence of other risk factors, including obesity among US children and adults, are cause for public health concern. Additionally, there is a lack of widespread utilization in the United States of preventive interventions, such as vaccination against cancer-causing pathogens, including HPV, which is the primary cause of cervical cancer.

Environmental risk factors, such as air pollution, water contamination, and naturally occurring radon gas, also increase a person's risk for certain types of cancers, such as lung cancer. There is also an increasing recognition that endocrine-disrupting chemicals, such as those found in hair straightening products, food packaging, and many other consumer products, can increase the risk of certain diseases, including cancers of the breast and thyroid.

Exposure to elevated levels of carcinogens in certain occupations, such as firefighting or welding, can increase the risk of certain types of cancer. Furthermore, occupations that involve night shift work, which can disrupt the body's natural sleep patterns, as well as the lack of sleep due to overwork, can increase an individual's risk of developing cancer. Finally, hormonal factors that result from normal physiology, such as pregnancy and breastfeeding can also increase or decrease the risk of developing certain types of cancer.

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

25% OF THE REDUCTION IN BREAST CANCER MORTALITY IN THE UNITED STATES FROM 1975 TO 2019 IS ATTRIBUTABLE TO ROUTINE MAMMOGRAPHY.
ESW5

Screening for Early Detection

Cancer screening refers to checking for cancer, or for abnormal cells that may become cancerous, in people who do not have any signs or symptoms of the disease. Cancer screening can help detect cancer at the earliest possible stage when it can be treated successfully, with a higher likelihood of cure. Accruing evidence shows that cancer screening saves lives and reduces the burden of the disease at a population level.

In the United States, the US Preventive Services Task Force, a panel of experts in preventive medicine, periodically issues evidence-based screening recommendations for cancers of breast, cervix, colon and rectum, lung and bronchus, and prostate. Key considerations that determine who should receive screening and for which cancer include biological sex and age of the individual, as well as genetic, environmental, behavioral, and social influences.

Cancer screening is a multistep process that includes receiving the recommended test, as well as follow-up care if the initial test shows abnormal findings. Unfortunately, disadvantaged segments of the US population experience inequities in receiving the recommended cancer screening and follow-up care. There are several reasons for low rates of cancer screening, including social and structural barriers; bias and discrimination against marginalized populations in the health care system; mistrust of health care professionals among minoritized populations; lack of access to quality health insurance; low health literacy; and miscommunication between patients and providers.

Researchers have identified evidence-based interventions that are proving effective in increasing adherence to recommended screening guidelines and follow-up care. These interventions include using electronic health records to educate and inform patients and providers about routine cancer screening; reducing structural barriers so that it is easier for people to take the routine cancer screening test; and implementing culturally tailored strategies to build trust between patients and providers.

Researchers are also cautiously optimistic about the potential of recent technological advances, such as implementation of artificial intelligence (AI) and minimally invasive screening tests, in improving early detection of cancers. In recent years, FDA has approved several AI-assisted medical devices to aid clinicians in cancer diagnosis. During the 12 months covered by this report (July 1, 2023–June 30, 2024), FDA also approved two minimally invasive tests for inherited risk prediction or early detection of cancer. These approvals underscore the potential of AI and minimally invasive screening tests to detect cancers early. However, large prospective studies are required to establish that these approaches will improve early detection of cancers without increasing harm for individuals and/or further exacerbating existing inequities in the receipt of cancer screening and follow-up care.

Inspiring Science. Fueling Progress. Revolutionizing Care.

The dedicated efforts of researchers working across the continuum of cancer science and medicine power breakthroughs in clinical care that are improving survival and quality of life for patients in the United States and around the world. Clinical trials are a vital part of medical research because they establish whether new cancer treatments are safe and effective. Therefore, it is imperative that participants in clinical trials represent the full spectrum of the patient population who may use these treatments if they are approved. Unfortunately, participation in cancer clinical trials is low, and there is a significant lack of sociodemographic diversity among those who do participate. It is imperative that researchers and policymakers work together to address the many barriers to clinical trial participation. Enhancing the availability of clinical studies, particularly in community settings, can be transformative for patients, as reflected in the personal story of **Dr. Humberto M. Guiot** (see p. 103).

Surgery, radiotherapy, and cytotoxic chemotherapy constitute three of the five main pillars of cancer treatment. However, these therapies can have long-term adverse effects on patients. Through ongoing clinical studies, researchers are evaluating whether less aggressive surgery, radiotherapy, and cytotoxic chemotherapy can be appropriate for some patients with cancer, allowing these patients to experience improved quality of life.

Among the advances made between July 1, 2023, and June 30, 2024, are the 15 new anticancer therapeutics approved for use by FDA. During the same period, FDA also approved a new imaging agent to aid breast cancer surgery and expanded the use of 15 previously approved anticancer therapeutics to treat additional cancer types.

Included in the FDA approvals are the first tumor-infiltrating lymphocyte-based cellular immunotherapy that is benefiting patients with advanced melanoma such as **Jennifer Ficko** (see p. 117), a new T cell–engaging

bispecific antibody against a novel target for patients with small cell lung cancer, the first AKT-targeted therapeutic for patients with breast cancer such as **Julia K. Levine** (see p. 99), the first KRAS-targeted therapy for certain patients with colorectal cancer, and several new molecularly targeted therapeutics and immunotherapeutics for the treatment of patients with an array of blood cancers, such as **Vicki W. Jones** (see p. 119) who is receiving a new molecularly targeted therapeutic to treat her multiple myeloma. While these exciting new advances have the potential to transform clinical care, much work is needed to ensure equitable access to these treatments for all patient populations.

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. As of January 2022, the most recent year for which such data are available, there were more than 18 million people living in the United States with a history of a cancer diagnosis, which equates to about 5 percent of the US population. This is a significant improvement from 50 years ago when cancer survivors constituted only 1.4 percent of the US population. Understanding and addressing the short- and long-term challenges faced by cancer survivors, supporting their quality of life, and ensuring that care is accessible and equitable are important priorities in cancer survivorship research.

Each person diagnosed with cancer has a unique experience ranging from successful treatment and living cancer free for the remainder of life to living a high-quality life through successful management of metastatic cancer to experiencing varying degrees of side effects to a subsequent cancer diagnosis with the same or a different type of cancer. Survivors often face physical, psychosocial, and financial challenges, both during and after the conclusion of treatment.

Cancer survivors should adhere to a healthy diet, engage in physical activity, reduce or eliminate the consumption of alcohol, and stop smoking, all of which help mitigate the physical challenges associated with a diagnosis of cancer. Researchers are also using other evidence-based strategies, including palliative care, pyscho-oncology, patient-reported outcomes, and patient navigation, to help reduce the adverse impact of a cancer diagnosis on the physical, mental, and financial health of cancer survivors. Understanding the survivorship challenges, as well as how to reduce or eliminate them, is an active area of research that is continually evolving as new therapies are introduced in the clinic.

Challenges experienced by patients and survivors of cancer also extend to friends and family members who often act as informal caregivers. There are an estimated four million caregivers who are caring for an adult cancer patient in the United States. These caregivers support cancer survivors in multiple ways, such as by arranging transportation for clinical appointments, helping with day-to-day activities, assisting in medical care or other clinical tasks, coordinating care, and providing emotional support. Caregiving often leads to burnout, which negatively impacts caregivers' psychological and emotional well-being. More evidence of the challenges faced by caregivers is emerging through ongoing research, which also highlights the many opportunities to assist this vulnerable population.

Envisioning the Future of Cancer Science and Medicine

Breakthrough discoveries and technological advances across the fields of medicine have substantially increased the understanding of cancer initiation and progression, providing the foundational knowledge for better strategies to reduce the risk of developing cancer, detect cancer at the earliest possible stage, and treat cancer effectively and more precisely. As a result, cancer deaths are declining, and survivors are living longer and fuller lives. Researchers, including AACR president, 2024-2025, **Patricia M. LoRusso, DO, PhD (hc), FAACR** (see p. 149), firmly believe that the fast-paced trajectory of progress against cancer can be further accelerated through sustained and predictable funding for cancer research.

Radiotherapy, one of the pillars of cancer treatment, has experienced a wave of innovation in the past decade, including delivering radiation precisely to tumors, thus minimizing harm to the surrounding normal tissues. Radiotheranostics is another promising technique for detecting and treating cancer using radioisotopes that has shown remarkable success

"The future of cancer science and medicine is promising. Cancer diagnostics are becoming more sophisticated. New technologies, such as spatial transcriptomics, are helping us study tumors at a cellular level. Artificial intelligence–based approaches are beginning to transform cancer detection, diagnosis, treatment decision making and response monitoring."

Patricia M. LoRusso, DO, PhD (hc), FAACR
AACR President, 2024–2025

against multiple cancer types, marking a significant advance in radiation-based cancer treatment.

Advances in non-invasive cancer imaging are revolutionizing visualization of tumor metabolism and assessment and monitoring of treatment response inside the body, thus enabling clinicians to make informed treatment decisions in a timely manner. Another exciting advance is the emergence of cancer engineering, a powerful interdisciplinary approach that combines principles from engineering, biology, and medicine for understanding the complexities of cancer development to improve health outcomes.

Advancing Cancer Research and Patient Care Through Evidence-based Policies

Sustained investments in medical research are critical for progress against cancer, including risk reduction, early detection, and treatment. As the largest public source of funding for medical research, NIH supports a vast array of scientific and educational programs that enable breakthroughs, which benefit human health and train the next generation of researchers. Within NIH, NCI leads the National Cancer Program and is the world's largest single supporter of cancer research and training.

Federal support is also needed to ensure that the benefits of medical research are shared by all populations. Achieving health equity requires further investments in NIH and NCI on cancer disparities research and in education and training programs to ensure that the cancer research and care workforce is broadly representative of society. Other key investments include FDA programs for improving access to and diversity of cancer clinical trials; CDC initiatives for building a robust public health infrastructure and programs to improve cancer screening and reduce the use of tobacco; and US Environmental Protection Agency (EPA) actions and environmental health policies for reducing environmental exposures to carcinogens.

In recent decades, cancer mortality rates have declined for many childhood cancers. However, further policy solutions are needed to continue to expand research on cancer in children and adolescents, improve data collection, and expand and increase access to clinical trials for children and AYA with cancer. Congress has begun considering several pieces of legislation to address these issues, but more work is needed to speed progress against childhood, AYA, and other rare cancers.

AACR Call to Action

From fiscal year FY 2016 to FY 2023, Congress increased NIH funding for eight consecutive years. These funding increases for medical research accelerated the pace of scientific progress and contributed to the longer-term decline in cancer mortality in the United States. Unfortunately, after years of growing federal budgets for medical research, Congress cut NIH funding in FY 2024. This budget reduction threatens to curtail the progress seen in recent years and stymie future advancements. AACR urges Congress to continue to support robust, sustained, and predictable funding growth for the medical research and health programs that are vital to the fight against cancer.

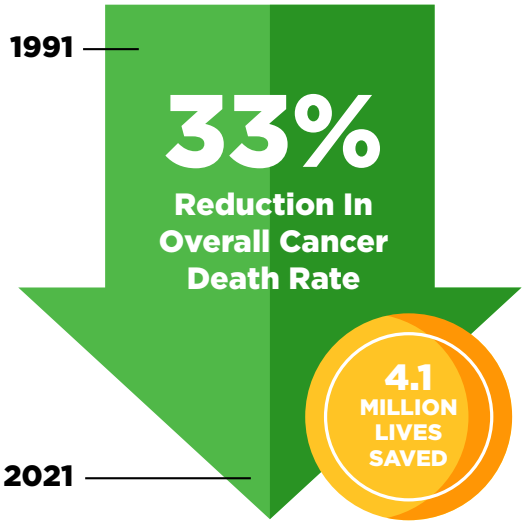
We call on Congress to:

- **Appropriate at least $51.3 billion in FY 2025 for the base budget of NIH** and at least $7.934 billion for NCI.
- **Provide $3.6 billion in dedicated funding for Cancer Moonshot activities** through FY 2026 in addition to other funding, consistent with the President's FY 2025 budget.
- **Appropriate at least $472.4 million in FY 2025 for the CDC Division of Cancer Prevention** to support comprehensive cancer control, central cancer registries, and screening and awareness programs for specific cancers.
- **Allocate $55 million in funding for the Oncology Center of Excellence at FDA** in FY 2025 to provide regulators with the staff and tools necessary to conduct expedited review of cancer-related medical products.

By following these recommendations, Congress will help speed the rate of discovery and create vital pathways for young scientists to contribute to future advances in cancer research. This investment will improve our nation's health, including the lives of the millions of people who have been affected by cancer.

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

Snapshot of a Year of Progress



Between July 1, 2023, And June 30, 2024, FDA Approved:

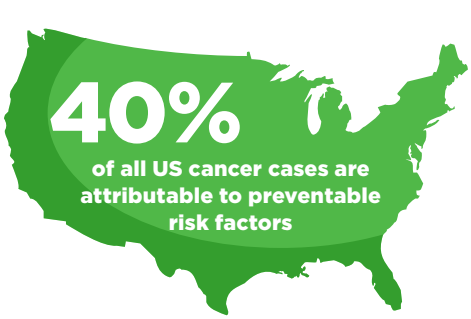
- **15** **New anticancer therapeutics**, which are now benefiting patients with various types of cancer
- **15** **Previously approved anticancer therapeutics** for treating new types of cancer
- **1** **New imaging agent**
- **2** **Minimally invasive tests** for assessing inherited cancer risk or for early detection of cancer
- **AI** **Several artificial intelligence (AI)-based tools** to improve early detection and diagnosis of cancers

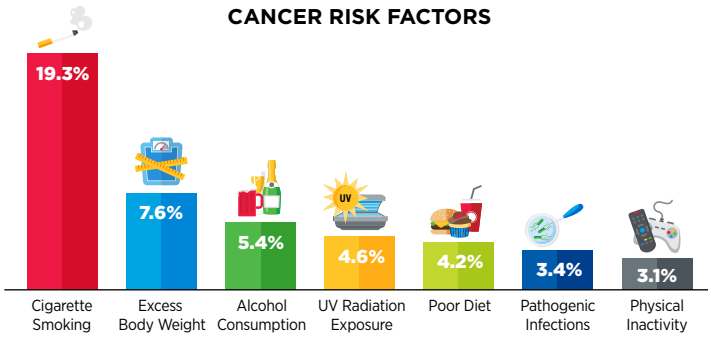
Research continues to advance immunotherapy, leading to:

- The first tumor-infiltrating lymphocyte-based cellular immunotherapy that is benefiting patients with advanced melanoma (see **Jennifer Ficko's** story, p. 117).
- The first approval of an immune checkpoint inhibitor for patients with a rare tumor of the head and neck which originates in the nasopharynx.
- Three new T cell-engaging bispecific antibodies for patients with multiple myeloma (see **Vicki W. Jones's** story, p. 119) and lung cancer.

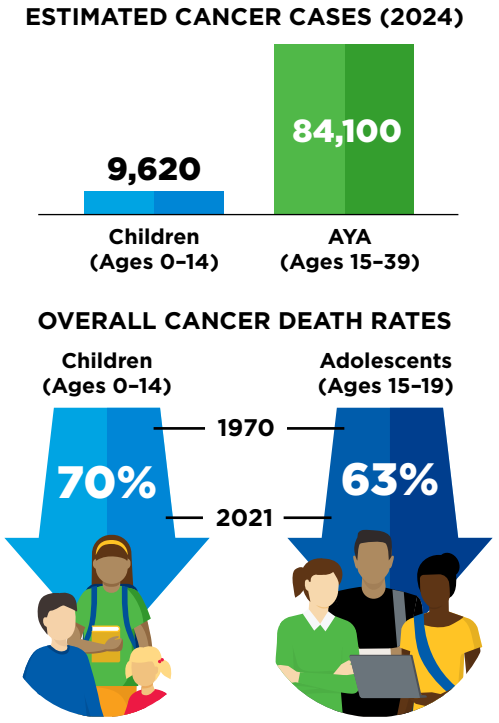
Research continues to harness the power of molecularly targeted therapy, leading to:

- A first-in-class AKT targeted therapeutic for patients with breast cancer, (see **Julia K. Levine's** story, p. 99).
- First approval of a KRAS targeted therapeutic for patients with metastatic colon cancer; the treatment may also benefit patients with advanced pancreatic cancer (see **Dr. Humberto M. Guiot's** story, p. 103).
- A new molecularly targeted therapeutic for desmoid tumors, an extremely rare and potentially debilitating condition.





Cancer in Children, Adolescents and Young Adults (AYA) in the US



FDA approved several anticancer drugs for children with cancer (July 2023–June 2024), including:

- Molecularly targeted therapeutics to:
  - Treat certain types of brain tumor (see **Michael Methner's** story, p. 125).
  - Reduce the risk of high-risk neuroblastoma relapse (see **Parker Shaw's** story, p. 127).
  - Treat a wide array of cancer types that have a specific genetic alteration known as *NTRK* gene fusion.
- Several molecularly targeted therapeutics and immunotherapeutics that were already approved for use in adults for the treatment of children with the same cancer types.

AYA cancer survivors (see **Lourdes Monje's** story, p. 137) face long term side effects; 40 percent experience multiple chronic health conditions (e.g., hearing loss, stroke, diabetes.)

Advances in Genomics Accelerating Progress Against Childhood Cancers

CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH CANCER

↓

TUMOR CHARACTERIZATION

Childhood Cancer Data Initiative*
Molecular Characterization Initiatives*

↓

Understanding biology
Fusion Oncoproteins in Childhood Cancers Consortium*

Assessing cancer risk

Genetic testing for surveillance

Treatment decisions
NCI–Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice Trial*

*NCI initiative.

Call to Action

For the Fiscal Year 2025, AACR urges Congress to continue to support robust, sustained, and predictable funding for the federal medical research and health programs vital to progress against cancer:

NIH	NCI	CDC's Division of Cancer Prevention and Control	FDA's Oncology Center of Excellence
$51.3 BILLION	$7.934 BILLION	$472.4 MILLION	$55 MILLION

Cancer in 2024

IN THIS SECTION, YOU WILL LEARN:

- In the United States (US), the overall cancer death rate has been steadily declining since the 1990s, with the reductions between 1991 and 2021 translating into more than 4.1 million cancer deaths avoided.
- 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.
- More than 18 million cancer survivors were living in the United States as of January 1, 2022.
- Progress has not been even 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.
- 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, regardless of their race, ethnicity, age, sexual orientation, gender identity, socioeconomic status, or geographic location.
- The economic burden of cancer on individuals and the US health care system 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 to accelerate the pace of progress against cancer.

Research: Driving Progress Against Cancer

Research is the foundation of progress against the collection of diseases we call cancer. It improves survival and quality of life for people around the world because it is the driving force behind every clinical breakthrough and every public policy designed to improve human health. Discoveries across the major areas of cancer research, including basic, clinical, translational, and population science, provide the foundation for advances in cancer prevention, early detection, diagnosis, treatment, and survivorship.

Every clinical advance and every policy that spurs progress against cancer is the culmination of a complex process that requires collaboration over the course of many years among numerous stakeholders (see **Sidebar 1**, p. 12).

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:

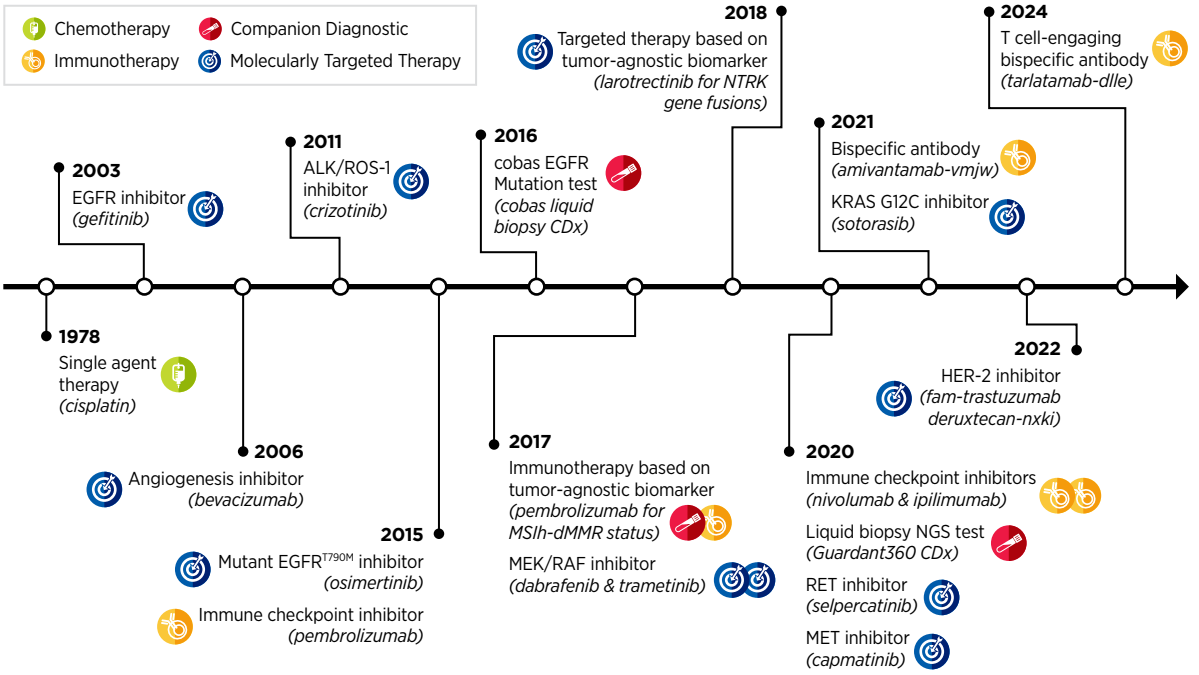
Source: (1).

The remarkable advances made against cancer—in particular, improvements in early detection, diagnosis, treatment, and risk reduction—are resulting in a steady decline in US cancer death rates year after year. In fact, the age-adjusted overall cancer death rate has fallen by 33 percent between 1991 and 2021, a reduction that translates into an estimated 4.1 million fewer deaths from cancer (2). The reduction in overall US cancer mortality rate can be attributed to significant reduction in smoking rates, as well as improvements in treatment and early detection of certain cancers.

FIGURE 1

Research Driving Progress Against Lung Cancer

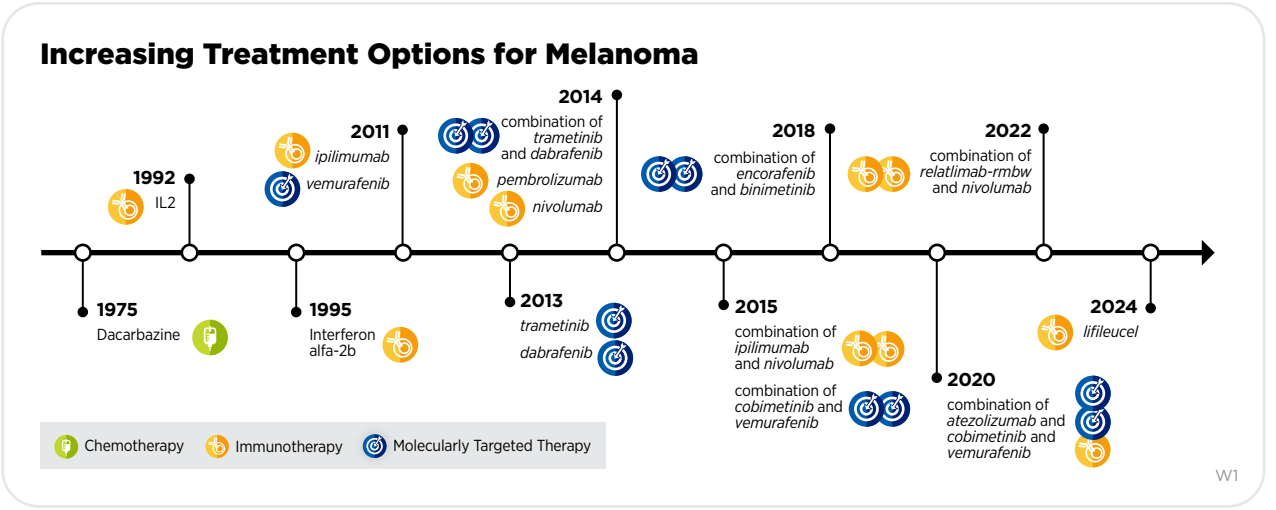
FIRST FDA APPROVALS OF THERAPEUTICS WITH DISTINCT MECHANISMS OF ACTION



Thanks to research-driven clinical breakthroughs and steep reduction in US smoking rate, lung cancer mortality is declining rapidly. In fact, the decrease in lung cancer mortality per year accelerated from 2 percent between 2005 and 2013 to 4 percent between 2013 and 2021 (4). Basic research discoveries have identified numerous cellular pathways that are associated with lung cancer development. Key components of these pathways include proteins such as KRAS, EGFR, FGFR, ALK, ROS1, RET, MET, NTRK, HER2, and DLL3. Research has also shown that cancer cells evade destruction by the immune system because they have high levels of proteins that can attach to and trigger brakes on immune cells, stopping them from attacking cancer cells. Collectively, this knowledge has laid the foundation for personalized treatments for patients with lung cancer, in particular, molecularly targeted therapeutics and immunotherapeutics, which have resulted in remarkable lasting responses. Indicated on the timeline are important milestones in lung cancer precision medicine, including first US Food and Drug Administration (FDA) approvals for molecularly targeted therapeutics or immunotherapeutics that have distinct mechanism of action. While not included in the figure, large scale clinical studies such as the National Lung Screening Trial and Nederlands–Leuvens Longkanker Screenings Onderzoek have demonstrated that early detection using low-dose computed tomography (LDCT) screening can lower lung cancer mortality (5,6). Population-level implementation of LDCT use (current uptake of which is extremely low) among eligible individuals can further reduce the burden of lung cancer in the United States.

Reduction in death rates for breast cancer among females and colorectal cancer among those over age 50 since the 1990s contributed to the progress in reducing overall US cancer mortality (2). According to a recent analysis, US breast cancer mortality declined by 42 percent, averting greater than 490,000 deaths between 1989 and 2021, because of advances in screening mammography and treatment (2). The death rate for colorectal cancer, overall, has declined by 39 percent between 2000 and 2022 (3). However, mortality has been rising among those diagnosed before the age of 50 (see **Cancer in Children, Adolescents, and Young Adults (AYA)**, p. 14).

The accelerated decline in overall cancer mortality in the past decade has been driven largely by rapid decreases in US lung



cancer death rates in both men and women, attributable to public health interventions to reduce smoking as well as advances in treatment (see **Figure 1**, p. 13) and early detection (3).

Research-driven advances in treatment have resulted in a steady decline in death rates despite increasing incidence for leukemia, melanoma, and kidney cancer (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 that have drastically improved outcomes for patients (7). Advances in the treatment of kidney cancer, in particular, with molecularly targeted therapeutics and immunotherapeutics have transformed clinical care for these patients. In fact, in a recent study, an immunotherapeutic, pembrolizumab (Keytruda), was shown to be the first postsurgical treatment that helps patients with early-stage kidney cancer live longer (8).

Among the major advances made across the clinical cancer care continuum from July 1, 2023, to June 30, 2024, are 15 new anticancer therapeutics that were approved for use by the US Food and Drug Administration (FDA) (see **Progress Across the Clinical Cancer Care Continuum**, p. 85). During this period, FDA also approved new uses for 15 previously approved anticancer therapeutics, a new imaging agent to help visualize cancerous cells during surgery, and several artificial intelligence (AI) based tools to improve early detection and diagnosis of cancers.

Collectively, advances such as these and those described in past editions of this annual report are helping to increase the number of children and adults who live longer and fuller lives after a cancer diagnosis. Indeed, the 5-year relative survival rate for all cancers combined has increased from 49 percent for those diagnosed in the mid-1970s to 69 percent among those diagnosed during 2013 to 2019 (4). As of January 1, 2022, more than 18 million individuals with a history of cancer were alive in the United States, and the number is projected to grow to 26 million by 2040 (9). Additionally, because of improved treatments, increasing numbers of individuals are now living longer despite being diagnosed with metastatic disease (10). Continued research to address the survivorship needs of the growing number of individuals living with cancer must be a priority for US medicine and public health (see **Supporting Cancer Patients and Survivors**, p. 129).

★ SPOTLIGHT

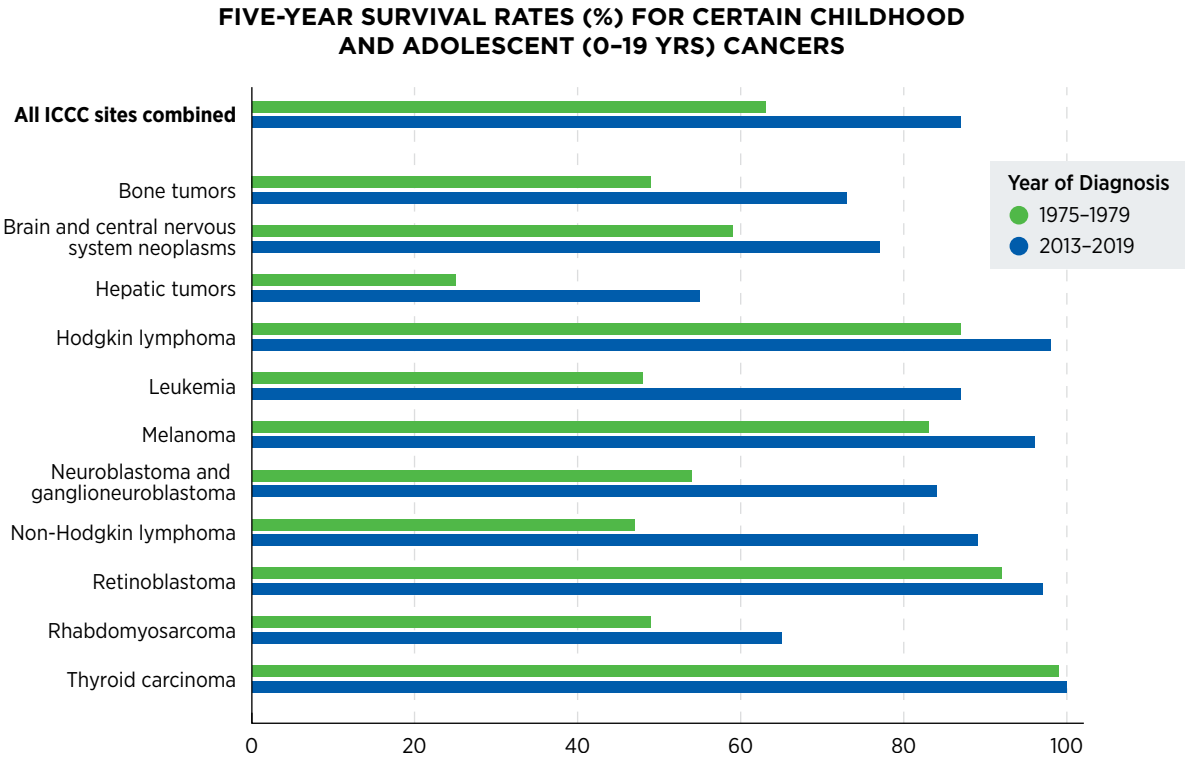
Cancer in Children, Adolescents, and Young Adults (AYA)

Compared to cancers in adults, cancers are rare in children, adolescents and young adults (AYA). In the United States in 2024, approximately 9,620 children (14 years and younger) and 5,290 adolescents (15 to 19 years) will be diagnosed with cancer (4). Leukemia and cancers of the nervous system, including brain tumors, are the most common cancers in children. Among adolescents, brain and nervous system tumors are the leading sites of new cancer cases, followed by lymphoma and leukemia. In contrast, young adults ages 20 to 39 years are most commonly diagnosed with solid tumors, including thyroid cancer, melanoma, and breast cancer.

Decades of research-driven advances in cancer science and medicine, including the identification and therapeutic targeting of cellular and molecular drivers of cancer (see **Research-driven Progress Against Childhood and AYA Cancers**, p. 115), along with progress in surgical techniques and optimization of radiotherapy and chemotherapy have led to a steady decline in cancer death rates for children and

★ 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 2013 to 2019 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 seen for all cancers combined as well as for several individual cancer types.

Source: (3).

AGE GROUPS	CANCER INCIDENCE RATE (PER 100,000)
Children (ages <15)	**17.1**
Adolescents and young adults (AYA) (ages 15–39)	**74.9**
Adults (ages 40–64)	**529**
Older adults (ages 65–74)	**1,753**

Source: (3).

W2

adolescents. Among US children (14 years and younger) and adolescents (15 to 19 years), overall cancer death rates have declined by 70 percent and 63 percent, respectively, between 1970 and 2021 (4). Just in the past two decades, the overall cancer death rate for children and adolescents declined by 24 percent (11).

The 5-year relative survival rate for all cancers combined has improved for US children from 58 percent during the mid-1970s to 85 percent for those diagnosed between 2013 and 2019 (4). However, there are significant differences in survival rates between different cancer types (see **Figure 2**, p. 15). Cancer survival has also improved for AYAs. Based on a recent study that evaluated survival trends across 33 common AYA cancers, those diagnosed between 2010 and 2018 had a 5-year relative survival of 86 percent (12). Of the 33 cancer types, 25 had significant improvement in 5-year

AN ESTIMATED 208,620
US ADOLESCENTS AND YOUNG ADULTS (AYA)
ARE LIVING WITH A BRAIN TUMOR DIAGNOSIS IN 2024.

Often referred to as central nervous system tumors, these cancers are the second leading cause of cancer-related death in AYAs and the **leading cause of death for those between 15 and 24 years old** (14).

W3

relative survival since 2000. However, AYAs had a much lower 5-year relative survival than children for four cancers, including acute lymphocytic leukemia (ALL) and Ewing sarcoma (12).

Despite the progress, cancer is the leading cause of disease-related death among US children, with around 1,040 children expected to die from the disease this year (4). Additionally, there are disparities in the burden of childhood and AYA cancers for racial and ethnic minority groups and other medically underserved populations in the United States. As one example, while the overall cancer death rate for White children and adolescents declined by 12 percent between 2011 and 2021, the rates did not change significantly for Black and Hispanic children and adolescents (11). Recent data also show that non-Hispanic Black AYAs experience worse survival for many cancers compared to other racial and ethnic groups (12).

Additionally, there are disparities based on socioeconomic status. For instance, children with cancer living in Alabama counties with persistent poverty during 2000–2016 were 30 percent more likely to die within 5 years of cancer diagnosis, compared to those not living in Alabama counties with persistent poverty (13).

Addressing the barriers that drive survival disparities in childhood and AYA cancers, such as lack of clinical trial enrollment, access to guideline-adherent treatments, and long-term survivorship care, as well as identifying biological features of these cancers is vital for continued progress.

While overall cancer incidence in the United States has stabilized in recent years, a rising concern among public health experts is the steadily increasing incidence of certain cancer types among individuals younger than 50 years, a phenomenon referred to as early-onset cancer. According to a recent report, the incidence of early-onset cancers, particularly among individuals aged 30 to 39 years, increased significantly during 2010 to 2019 (15). In 2019, most early-onset cancers were diagnosed in the breast, thyroid, colon, and rectum (15). Between 2010 and 2019 the greatest increase in early-onset cancer occurred for those arising in the gastrointestinal system. In fact, many studies have reported an increase in the incidence of early-onset colorectal cancer (16,17). According to a recent report, between 2011 and 2019, colorectal cancer incidence rates increased by 1.9 percent per year in people younger than 50 years (16,18).

Another cancer for which the incidence rate has been rising in US young adults is cervical cancer (19,20). Specifically, a recent analysis revealed that cervical cancer incidence among women ages 30 to 34 years increased by 2.5 percent per year between 2012 and 2019 (20). Considering that cervical cancers are largely preventable—most cases are caused by infection with human papillomavirus (HPV), and HPV vaccination (see **Prevent and Eliminate Infection From Cancer-causing Pathogens**, p. 54) and cervical cancer screening are extremely effective in reducing the burden of cervical cancer—these data emphasize the critical importance of public health measures to boost cervical cancer prevention and early detection in the United States (see **Screening for Early Detection**, p. 63).

In this regard, research has shown that in young women who were most likely to have received the HPV vaccines, cervical cancer incidence is declining rapidly. As one example, in women aged 20 to 24 years, invasive cervical cancer incidence decreased by 65 percent from 2012 to 2019 compared to only by 24 percent from 2005 to 2012 (2).

Cancer: An Ongoing Challenge

Although incredible progress has been made against cancer, it continues to be an enormous public health challenge in the United States and around the world. In the United States, an estimated 2,001,140 new cases of cancer will be diagnosed in 2024 and 611,720 people will die from the disease (see **Table 1**, p. 17). Men have a higher incidence of many cancer types, including bladder, colon, and brain cancer, compared to women, and ongoing research is evaluating the role of a range of biological factors including genetics, epigenetics, metabolism, and immunity in mediating the sex differences in cancer burden (21-23).

In addition, many population groups in the United States experience disproportionately high rates of cancer incidence and death that are attributable largely to structural and socioeconomic

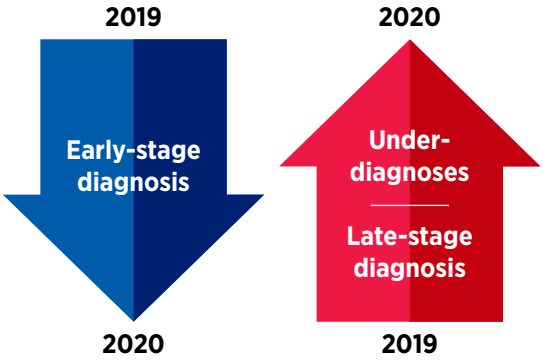
TABLE 1

Estimated Burden of Common Types of Cancer in the United States in 2024

	NEW CASES	DEATHS
All Cancers Combined	**2,001,140**	**611,720**
Breast	313,510	42,780
Prostate	299,010	35,250
Lung and Bronchus	234,580	125,070
Colorectal	152,810	53,010
Melanoma (Skin)	100,640	8,290
Bladder	83,190	16,840
Kidney and Renal Pelvis	81,610	14,390
Non-Hodgkin Lymphoma	80,620	20,140
Uterine	67,880	13,250
Pancreatic	66,440	51,750
Thyroid	44,020	2,170
Liver and Intrahepatic bile duct	41,630	29,840
Myeloma	35,780	12,540

Source: (3).

COVID-19 caused significant disruption of cancer care



These adversities were particularly severe among racial and ethnic minority groups and other medically underserved patients.

Source: (28).

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disadvantages. It should also be noted that current estimates of the cancer burden do not reflect the adverse impact of COVID-19, which caused declines in screening, early detection, new cancer diagnoses, and delays or discontinuations in cancer treatment, especially for medically underserved populations (24-27). Ongoing monitoring of cancer-related data at a population level is warranted to assess the long-term consequences of COVID-19 for cancer burden in the United States.

Inequities in the Burden of Cancer in the United States

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

Cancer disparities are one of the most pressing public health challenges in the United States. The National Cancer Institute (NCI) defines cancer disparities as adverse differences in cancer-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. 18).

As detailed in the *AACR Cancer Disparities Progress Report 2024* (29), US racial and ethnic minority groups and other medically underserved populations shoulder a disproportionately higher burden of cancer (see **Sidebar 3**, p. 19). As one example, during 2017–2021, the incidence rate for all cancers combined was higher among American Indian and Alaska Native (AI/AN) people compared to non-Hispanic (NH) White people (3). During the same time, overall cancer mortality rates were higher among Black and AI/AN individuals compared to NH White individuals. Additionally, during 2014–2020, patients with cancer from all racial and ethnic minority groups had a lower 5-year relative survival compared to NH White people (3).

There has been progress in reducing cancer disparities in recent years. As one example, the gap in overall cancer death rates between Black and White populations has narrowed by more than 50 percent over the past two decades (3). However, Black individuals still had a 9 percent higher overall cancer death rate compared to White individuals, and the highest death rate from cancer among all US racial or ethnic groups, in 2022 (3).

Researchers studying the science of cancer disparities are increasingly recognizing the heterogeneity in the cancer burden within each of the major racial or ethnic minority groups. As one example, striking disparities in cancer burden

SIDEBAR 2

US Population Groups That Experience Cancer Disparities

According to the National Cancer Institute (NCI), 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 (SES), including low educational attainment

Individuals who lack or have inadequate health insurance coverage

Individuals belonging to sexual and gender minority communities

Individuals with disabilities

Adolescents and young adults (AYA) (Ages 15–39)

Individuals who are incarcerated

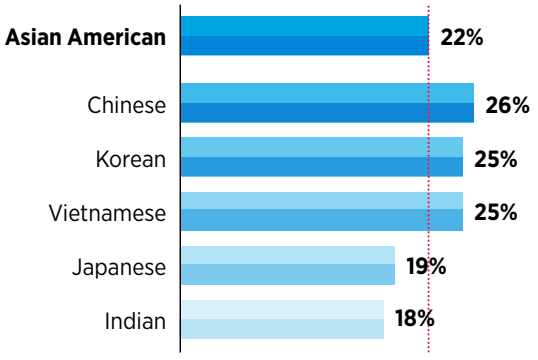
Immigrants, refugees, or asylum seekers

Older adults (Ages 65+)

Citizens of sovereign Native Nations

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

Deaths from all cancers combined are higher among Chinese, Korean, and Vietnamese subgroups and lower among Japanese and Indian subgroups compared to an aggregated Asian American reference group.



Source: (37).

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have been identified within Asian subpopulations and between Native Hawaiian or other Pacific Islander (NHOPI) and Asian individuals (29). 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. However, Asian and NHOPI populations continue to be grouped together in cancer epidemiologic data.

Stark differences in cancer incidence and outcomes have also been observed within the AI/AN populations when cancer data are disaggregated by geographic location. Research has shown that among AI/AN individuals, Indigenous Alaskans had the highest incidence of colorectal cancer between 2014 and 2018, compared to any other US racial population (36). The colorectal cancer incidence among Indigenous Alaskans was in fact the highest in the world in 2018 (36). These findings indicate that collection of disaggregated data is a vital step to

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 is detailed in *AACR Cancer Disparities Progress Report 2024* (29).

40% more likely	**BREAST CANCER MORTALITY** Black women with breast cancer are nearly 40 percent more likely to die from it compared to White women with breast cancer (3).
16% and 9% less likely	**5-YEAR SURVIVAL** Black and Latino individuals with lung cancer are 16 percent and 9 percent less likely, respectively, to survive 5 years after their diagnoses compared to White individuals (30).
79% and 98% higher	**KIDNEY CANCER INCIDENCE** The incidence of kidney cancer is 79 percent higher among non-Hispanic American Indian/Alaska Native (AI/AN) men and 98 percent higher among non-Hispanic AI/AN women compared to non-Hispanic White men and women (31).
12% and 13% higher	**TOBACCO-ASSOCIATED AND HPV-ASSOCIATED CANCER INCIDENCE** The incidence of tobacco-associated cancers and human papillomavirus (HPV)-associated cancers are 12 percent and 13 percent higher, respectively, among rural populations compared to their urban counterparts (32).
1.73X and 2.26X more likely	**CANCER IN SEXUAL AND GENDER MINORITY POPULATIONS** Gay men are 1.73 times more likely to be diagnosed with cancer than heterosexual men, while lesbian women are 2.26 times more likely to be diagnosed with cancer than heterosexual women (33).
18-21% and 64-69% higher	**PATIENTS WITH DISABILITIES** The likelihood of dying from gastric cancer is 18 percent to 21 percent higher in patients with disabilities and 64 percent to 69 percent higher in patients with severe disabilities, compared to individuals without disabilities (34).
7.1% higher	**PERSISTENT POVERTY** During 2014–2018, deaths from all cancers combined were 7.1 percent higher in counties experiencing persistent poverty compared to counties not experiencing persistent poverty (35).

fully understanding cancer disparities and developing effective strategies for achieving health equity.

In addition to racial and ethnic minority groups, many segments of the US population shoulder a disproportionate burden of cancer. These include residents in rural areas that lack access to cutting-edge cancer treatments and/or state-of-the-art health care facilities, sexual and gender minorities (SGM) who experience bias and discrimination in health care settings, and low-income households in counties with persistent poverty and limited access to healthy food and/or the needed health care. In addition, older adults, veterans, undocumented immigrants and refugees, individuals with disabilities, individuals who are incarcerated, adolescents, and young adults all are medically underserved to varying degrees and face unique challenges in the burden of cancer.

It should be noted that patients with intersectional identities, for instance, racial or ethnic minority patients from SGM communities, often experience multilevel barriers to cancer care that adversely impact screening, diagnosis, treatment, and survivorship. As another example, older adults (age 65 or older) with cancer often experience multilevel barriers to cancer care and those living in rural areas have an even greater burden—more likely to die within 1 year of cancer diagnosis—compared to those living in urban areas (38).

Cancer disparities are driven by complex and interrelated factors. Systemic inequities resulting from a long history of racism and contemporary injustices in the United States continue to have lasting, multigenerational adverse effects on marginalized populations in all aspects of life, including on health outcomes. Researchers use various frameworks to understand and address the influences that affect health outcomes and contribute to health disparities, including cancer disparities. These frameworks integrate influences from structural factors and include the interplay of biological factors, mental health, and modifiable risk factors (e.g., smoking and diet) with nonclinical factors called social drivers of health (SDOH) (39,40).

According to NCI, SDOH, sometimes also called social determinants of health, are the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and get older that can affect their health, well-being, and quality of life. Social drivers of health 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. 21).

A major social driver of cancer disparities is inadequate access to quality health care. Health insurance is a key determinant of whether individuals receive the needed health care. In 2021, nearly 27 percent of US adults ages 18 to 64 who were uninsured delayed or did not receive needed medical care, compared to a little over 7 percent of those who had either public or private insurance (41). A substantial proportion of racial and ethnic minorities and medically underserved populations in the United States lack health care access (29). Individuals lacking health insurance are less likely to be up to date with recommended cancer screening and are more likely to be diagnosed with cancer at an advanced stage (29). Uninsured patients are also less likely to receive needed treatments and more likely to experience worse cancer outcomes compared to privately insured patients (42-45).

Considering that a significant proportion of the US population is affected by cancer disparities, it is important that public health experts intensify efforts designed to improve the understanding and mitigation of these inequities. Only with new insights obtained through innovative and inclusive science, such as basic research assessing the effects of chronic stress and using biospecimens from diverse populations, clinical studies involving participants from all sociodemographic backgrounds, and health care delivery and implementation research that is representative of every community, will we be able to achieve health equity for all populations.

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 illustrated by the fact that the 5-year relative survival rates for US patients vary widely depending on both the type of cancer diagnosed and the stage at diagnosis (3). For example, the overall 5-year relative survival rates of 91 percent for patients with breast cancer and nearly 98 percent for patients with prostate cancer stand in stark contrast to the overall 5-year relative survival rates of 13 percent for those with pancreatic cancer or 8 percent for those with glioblastoma multiforme (GBM), an aggressive form of brain cancer (3).

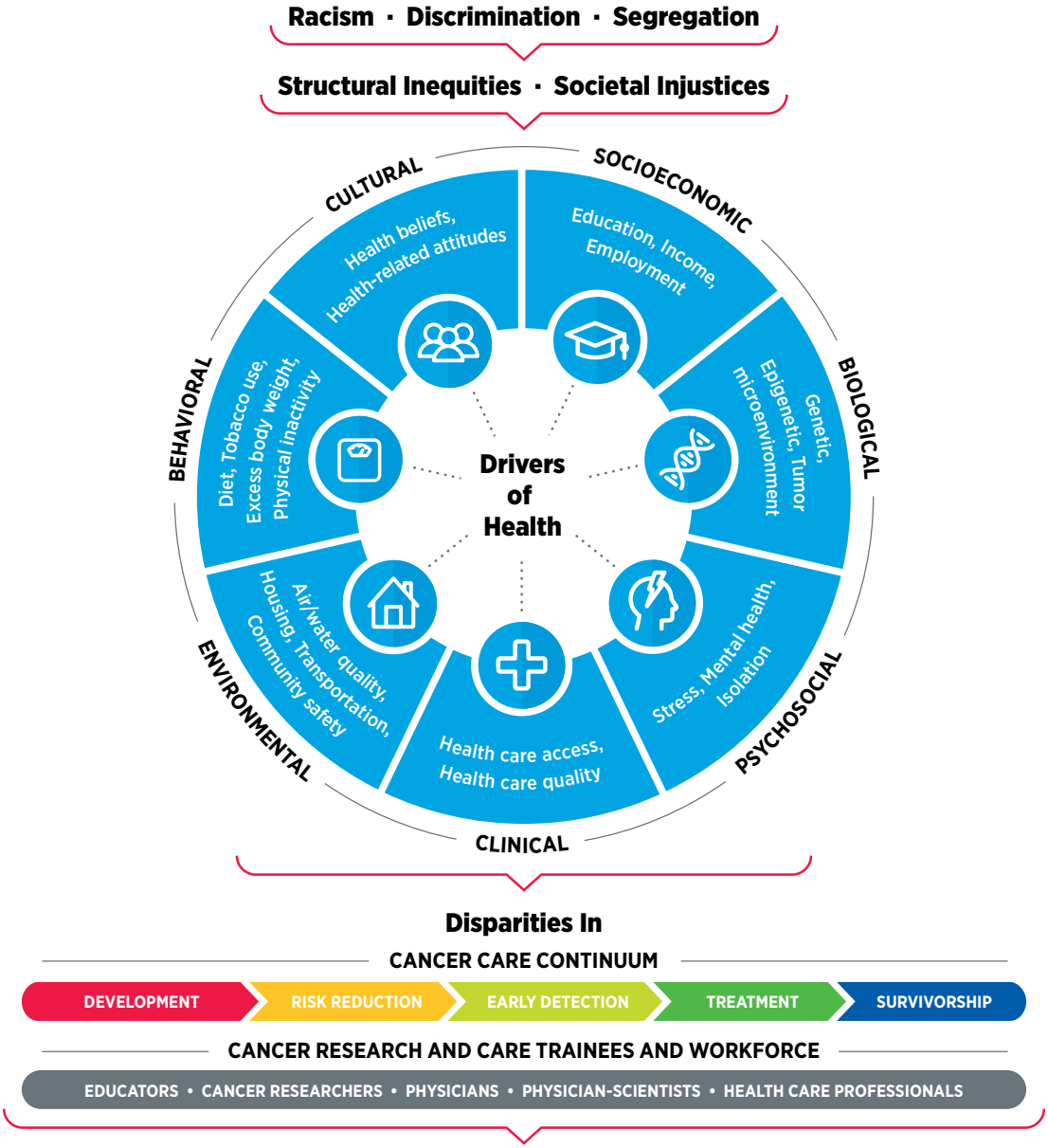
In addition, among women with breast cancer and men with prostate cancer, those with early-stage disease, i.e., whose cancer is confined to the breast, or to the prostate, have 5-year relative survival rates of almost 100 percent, while those whose cancer has spread to other organs the 5-year relative survival rates are 32 percent and 37 percent, respectively (3). Notably, the greater 5-year survival among individuals whose cancers were caught early through screening can be partly attributed to lead time bias, a phenomenon where early diagnosis falsely makes it appear that people are surviving longer (see **Screening for Early Detection**, p. 63).

Variable progress against different cancer types can be accredited in part to disparities in lifesaving therapeutic options that are available for different cancer types. As an example, just in the past decade, FDA has approved 14 molecularly targeted therapeutics and two immunotherapeutics for the treatment of patients with breast cancer. As a result, patients have a deep selection of therapeutics to choose from and breast cancer mortality has been declining steadily; between 2013 and 2022 the breast cancer death rate fell by an average of 1.2 percent per year (3). In contrast, progress has been slow for patients with GBM. Since the approval of the chemotherapeutic temozolomide nearly 25 years ago, no new anticancer agents have shown promise in improving overall survival. Consequently, the 5-year relative survival rate for patients with GBM remains at a dismal 8 percent (3).

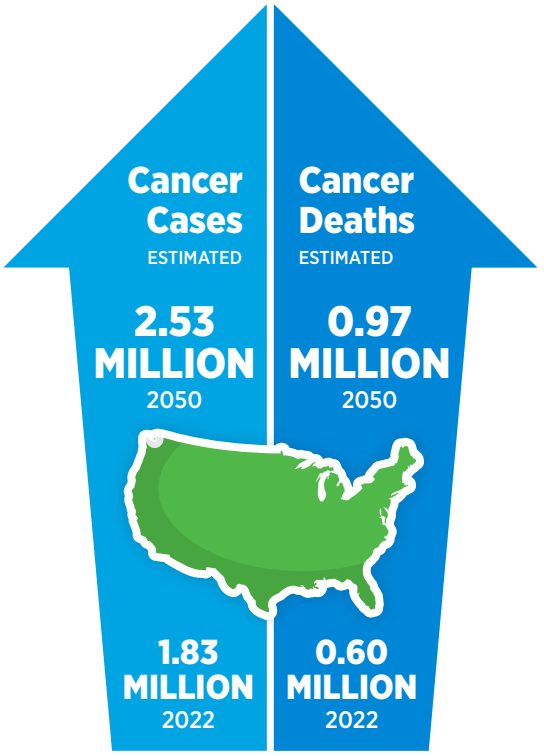
Developing new and effective tests for the early detection of more cancer types (see **Screening for Early Detection**,

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 known as social determinants of health, as the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and get older that can affect their health, well-being, and quality of life. Social drivers of health 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 the complex and interconnected key drivers of health and how they influence 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).



Source: (46).

W6

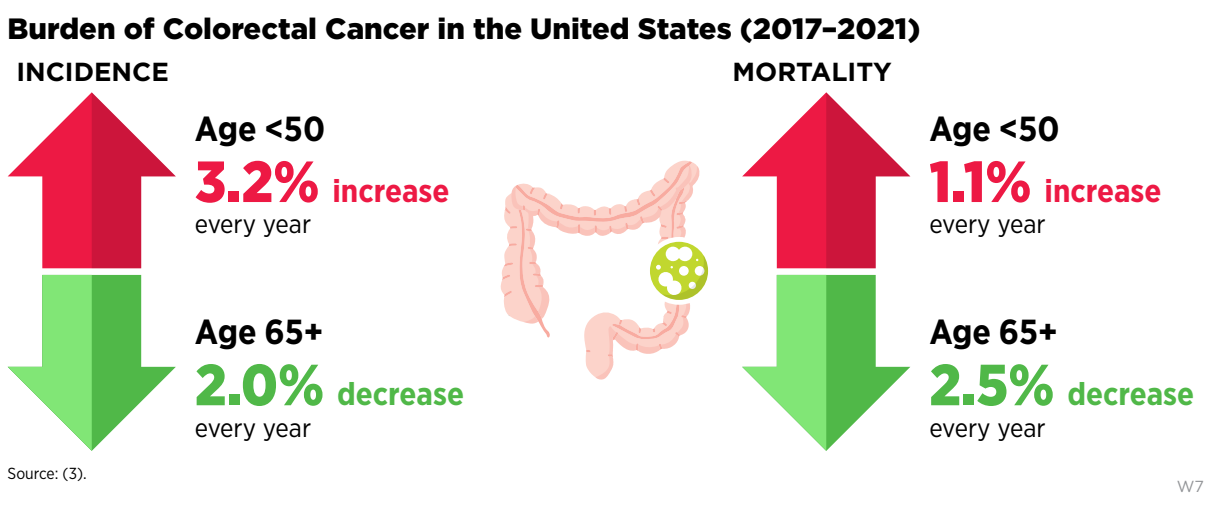
p. 63) could also help address the challenge of variable progress between types of cancer because the likelihood of a cure is much higher when cancer is diagnosed at an early stage when it is confined to its original location and has not spread to distant sites. Additionally, intensive research to uncover currently unknown biological drivers of cancer initiation and progression is needed to identify novel targets and improve therapeutic options for hard-to-treat cancers.

The Growing Population Burden of Cancer

The public health challenges posed by cancer are predicted to grow considerably in the coming decades unless we develop and implement more effective strategies for cancer prevention, early detection, and treatment. In the United States alone, the number of new cancer cases diagnosed each year is expected to surpass 2.5 million by 2050 (46). This is because cancer is primarily a disease of aging; 57 percent of diagnoses occur among those 65 and older (2), and this segment of the US population is expected to grow from 57.8 million in 2022 to more than 82 million in 2050 (47).

Also contributing to the projected increase in the number of US cancer cases are the high rates of excess body weight, physical inactivity, and alcohol consumption (48) and the continued use of cigarettes by 11.5 percent of adults (49) (see **Reducing the Risk of Cancer Development**, p. 43). Furthermore, a significant proportion of lung cancers (16 percent in women and 10 percent in men) are diagnosed in individuals without a history of smoking (50) and there is an urgent need for more research to understand the increasing trends of lung cancer incidence among those without a history of smoking (51). In this regard, a recent study showed that in Asian and Pacific Islander adults who never smoked, lung cancer incidence increased by an average of 2 percent per year between 2007 and 2018, while rates were stable in other US racial and ethnic groups (52). Identification of risk factors, a deep characterization of their disease, and the development of evidence-based early detection and treatments are critical needs to lower the burden of lung cancer in this population of patients who do not have a history of smoking.

While overall cancer incidence in the United States has stabilized in recent years, the incidence of certain cancer types as well as the age- and sex-specific incidence of certain cancers is increasing. For example, the incidence of pancreatic cancer, uterine cancer, and HPV-associated oral cancers has



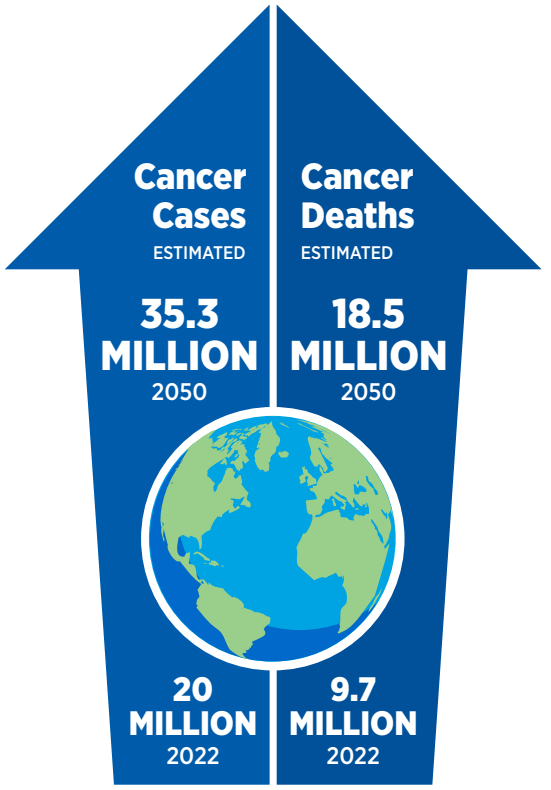
Source: (3).

W7

been rising (2). While the overall incidence of lung cancer is declining in the United States, young and middle-aged women are being diagnosed at a higher rate than their male counterparts (53). Based on a recent study, the decline in lung cancer incidence between 2000–2004 and 2015–2019 was greater in men ages 35 to 54, leading to a higher incidence in women ages 35 to 54 (53). This is a reversal of the historical trend of a higher incidence among men and cannot be attributed to smoking prevalence.

Researchers predict that US individuals born between 1965 and 1980 (Generation X) will have a higher incidence of cancer as they turn 60 or older compared to prior generations born between 1908 and 1964 (54). While the reasons are unclear, researchers believe that these increases could be attributable to many factors, including increased prevalence of modifiable risk factors, such as excess body weight, physical inactivity, and environmental pollutants. Additionally, as discussed previously, an increasing concern among public health experts is the rising incidence of early-onset colorectal cancers. Many of the early-onset colorectal cancer cases are also diagnosed at an advanced stage.

Understanding the reasons behind rising cases of early-onset cancers is an area of intensive research. 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 **Screening for Early Detection**, p. 63). Researchers are also evaluating new and improved strategies including genetic testing and minimally invasive testing for prevention and early detection of cancers in the younger population (18).



Source: (46).

W8

The Global Burden of Cancer

Beyond the United States, cancer is an ongoing global challenge. According to a recent analysis, there were an estimated 20 million new cancer cases and over 9.7 million deaths from cancer in 2022 (55). An estimated 53.5 million people were alive within 5 years following a cancer diagnosis. Cancers of the lung, breast, colon and rectum, prostate, and stomach are the five most frequently diagnosed cancers worldwide. Diseases accounting for the most cancer deaths globally are cancers of the lung, colon and rectum, liver, breast, and stomach.

There are stark disparities in the cancer burden among countries having 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.

A striking example of global disparities is the burden of breast cancer. In countries with a very high HDI, one in 12 women will be diagnosed with breast cancer in their lifetime and one in 71 women will die of it (55,56). These statistics are significantly worse in countries with a low HDI, where although fewer women are diagnosed (one in 27 women) with breast cancer in their lifetime, there is a much higher likelihood of dying from it (one in 48 women) (55). One of the drivers of these disparities is the fact that more patients from lower income countries are diagnosed with breast cancer at a later stage compared to higher income countries. According to a new study, up to 30 percent of women with breast cancer in sub-Saharan African countries were diagnosed with late-stage tumors compared to less than 10 percent of women with breast cancer in North America or Europe (57). Another example of global disparities in cancer burden is the widespread late diagnosis of prostate cancer along with the shortage of specialist surgeons and radiotherapy facilities in lower income countries, leading to worse outcomes for these patients (58).

NEARLY 70%

Nearly 70 percent of the **years of lives lost due to premature deaths from cancers** globally **could be averted** by applying **effective risk reduction** efforts and **improving access to curative treatments**.

Source: (59).

W9

An emerging concern among public health experts is the dramatic rise since the 1990s in the incidence of early-onset cancers, including cancers of the breast, colon, esophagus, kidney, liver, and pancreas, among others, around the world (60). According to a new analysis of 29 cancer types in 204 countries, the global incidence of early-onset cancers increased by 79 percent and the number of early-onset cancer deaths increased by 28 percent between 1990 and 2019 (61). Furthermore, the incidence of and deaths from early-onset cancer are projected to increase by 31 percent and 21 percent, respectively, between 2020 and 2030.

Researchers hypothesize that early life exposures to certain cancer risk factors (see **Reducing the Risk of Cancer Development**, p. 43) that have become more prevalent in recent decades, including diets rich in highly processed foods, alcohol, tobacco, sedentary lifestyle, obesity, environmental carcinogens, and an unfavorable microbiome, are playing a role in the increased incidence of early-onset cancers. Accordingly, it is critical for each country and region to conduct studies to understand the etiologies of early-onset cancers, and to tailor public health strategies based on the local characteristics and burden of early-onset cancers.

To ensure equitable progress against cancer worldwide, it is imperative that global medical research communities work together and share best practices to implement new and more effective strategies that incorporate local needs and knowledge into tailored national cancer control plans. Additionally, global cancer research funding needs to align with the distribution of cancer burden and treatment availability worldwide.

Public health experts have identified several priorities based on present and future needs of low-resource countries, including reducing the burden of advanced cancers; improving access, affordability, and outcomes of treatment; utilizing value-based care; fostering implementation research; building research capacity; and leveraging technologies to improve cancer control. Global cancer control efforts must also maximize opportunities to reduce the burden of infection-related cancers through prevention and/or treatment. Robust investment in cancer surgery and radiotherapy research is critical as they still play key roles in curative treatments of many solid tumors (62).

Deploying resources to raise public awareness of cancer prevention and mobilizing key stakeholders worldwide to work with national governments to prioritize vaccination against human papillomavirus (HPV) and hepatitis B virus (HBV) and treatment for hepatitis C virus (HCV) and *H pylori* can accelerate the pace of progress in reducing the global cancer burden (see **Reducing the Risk of Cancer Development**, p. 43). Investments in mitigating modifiable cancer risk factors including smoking, diet, and excess body weight can avert many future cancer diagnoses, leading to immense health and economic benefits globally. The urgent need for robust worldwide investments in cancer science and medicine is further emphasized by recent findings that estimated the cumulative global economic burden of cancer from 2020 to 2050 to be at an enormous $25.2 trillion (63).

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 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 (2). Unfortunately, these numbers stand in stark contrast to the NCI budget of $6 billion for the same year. Notably, the direct medical costs do not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, which are also extremely high. As one example, the costs of lost productivity for US AYA patients diagnosed with cancer in 2019 were an estimated $18 billion over their lifetime (64).

Patients with cancer shoulder a large amount of the economic burden associated with cancer care. In 2019, in the United States, patients with cancer lost nearly $5 billion due to time costs—the value of time that patients spend traveling to and from health care, waiting for care, and receiving care—and paid an estimated $16.2 billion in out-of-pocket costs for cancer care (65).

With the number of cancer cases projected to increase in the coming decades, it is likely that both direct and indirect costs will escalate. According to a recent report, the economic burden of cancer in the United States will reach $5.3 trillion over the next three decades (63). The rising personal and economic burden of cancer underscores the urgent need for

more research that will accelerate the pace of progress and curb the increasing burden of cancer.

Recent advances in cancer prevention, detection, and treatment, many of which are highlighted in this report and the 13 prior editions, were made as a direct result of the cumulative efforts of researchers from across the spectrum of cancer science and medicine. Much of their work, as well as that of FDA and CDC, is supported by funds from the federal government. Public sector funding from NIH and NCI contributes significantly to the development of novel anticancer drugs (66,67). The rapid pace of approval of cutting-edge precision cancer medicine, many of which were evaluated in NCI-funded clinical trials, has transformed the treatment landscape and dramatically improved patient outcomes. Researchers estimate that over the past 40 years, patients with cancer in the United States have gained 14 million years of additional life because of NCI-funded clinical trials (68). Therefore, the vital importance of federal investments in medical research in driving progress against cancer and saving lives cannot be overstated.

The consecutive increases in the NIH budget over the past decade have helped maintain the momentum of progress against cancer and other diseases. Additionally, NIH research grants help sustain the US economy. In fiscal year (FY) 2023, the $37.81 billion awarded to researchers in the 50 US states and the District of Columbia supported 412,041 new jobs and yielded $92.89 billion in economic activity (see **Investments in Research for a Healthier Future**, p. 154). Furthermore, robust funding for NIH helps ensure that the United States continues to be a global leader in medical research and innovation.

The decline in NIH funding in FY 2024 compared to FY 2023 and the uncertainty of the current budgetary environment as the FY 2025 appropriations unfold is therefore of grave concern to the medical research community. A lack of funding may deter early-stage scientists and those from racial or ethnic minority and other underrepresented population groups from choosing academic research as their career paths, which will impede progress against cancer.

It is imperative that in the years ahead, Congress continues to provide sustained, robust, and predictable increases in investments in the federal agencies that fuel progress against cancer, in particular, NIH, NCI, FDA, and CDC (see **AACR Call to Action**, p. 168). Such investments will help the medical and public health research community sustain the momentum of scientific and technological innovation and will accelerate the pace of progress against cancer to achieve the President's Cancer Moonshot goal of reducing US cancer death rates by at least 50 percent by the year 2047, supported by policymakers like **The Honorable Jamie Raskin** (see p. 25).

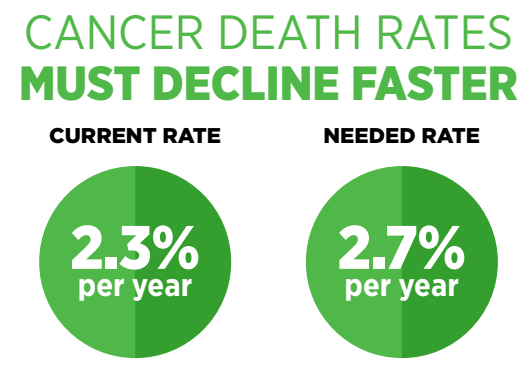
The Honorable Jamie Raskin

US REPRESENTATIVE FOR MARYLAND'S 8TH DISTRICT

Cancer has touched the lives of millions of Americans, including my own. As a survivor of both lymphoma and colorectal cancer, I am profoundly grateful to and inspired by the research community spearheading breakthroughs in cancer screening, prevention, treatment, and care. I'm proud to represent Maryland's Eighth District in Congress, home to the National Institutes of Health and many of our country's leading medical research experts, and I'm committed to serving as a congressional partner to advance cancer research: fighting in Congress for increased federal investment and supporting whole-of-government initiatives like President Biden's Cancer Moonshot. To the scientists and physicians working on the frontlines of the fight: thank you. Your service and scholarship provide us comfort and light the way towards a cure.

I recently did my one-year post-chemo checkup—my pet-scan, my cat-scan, my dog-scan, everything! And so far, so good, I'm hanging tough and feel extremely grateful to Dr. Roswarski and the whole team at Georgetown. I'm especially thrilled by the remarkable progress being made in cancer research and detection of all kinds. We should view medical and scientific research as central to our national security and health.

TO ACHIEVE THE CANCER MOONSHOT GOAL OF REDUCING OVERALL US CANCER DEATH RATES BY 50% BY 2047



Source: (70).

W10

Understanding the Path to Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- Cancer is a group of diseases in which some of the body's cells acquire changes that cause them to divide unchecked and spread to other parts of the body.
- Basic research plays a pivotal role in understanding how cancer develops and spreads.
- Changes inside the cell as well as in the tumor environment can influence cancer initiation and progression.
- Breakthroughs in technological advances have accelerated the identification of mechanisms that drive cancer.
- Integrating the knowledge of various aspects of cancer development has fueled the field of personalized medicine.

Precise molecular mechanisms control the growth and multiplication of normal cells. In cancer, these processes go awry, causing cells to divide uncontrollably and spread to other parts of the body. Cancer is a collection of related diseases that can affect almost any part of the body. During the course of cancer development, abnormal or damaged cells acquire characteristics that distinguish cancer cells from normal cells.

Hallmarks of cancer cells include their ability to multiply unchecked; acquire changes that make their genome unstable; ignore signals that stop normal cells from dividing or trigger death in old or damaged cells; utilize different metabolic strategies to sustain rapid growth; accumulate multiple genetic changes; leave the tissue of origin and spread to other sites; 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. 27) (71).

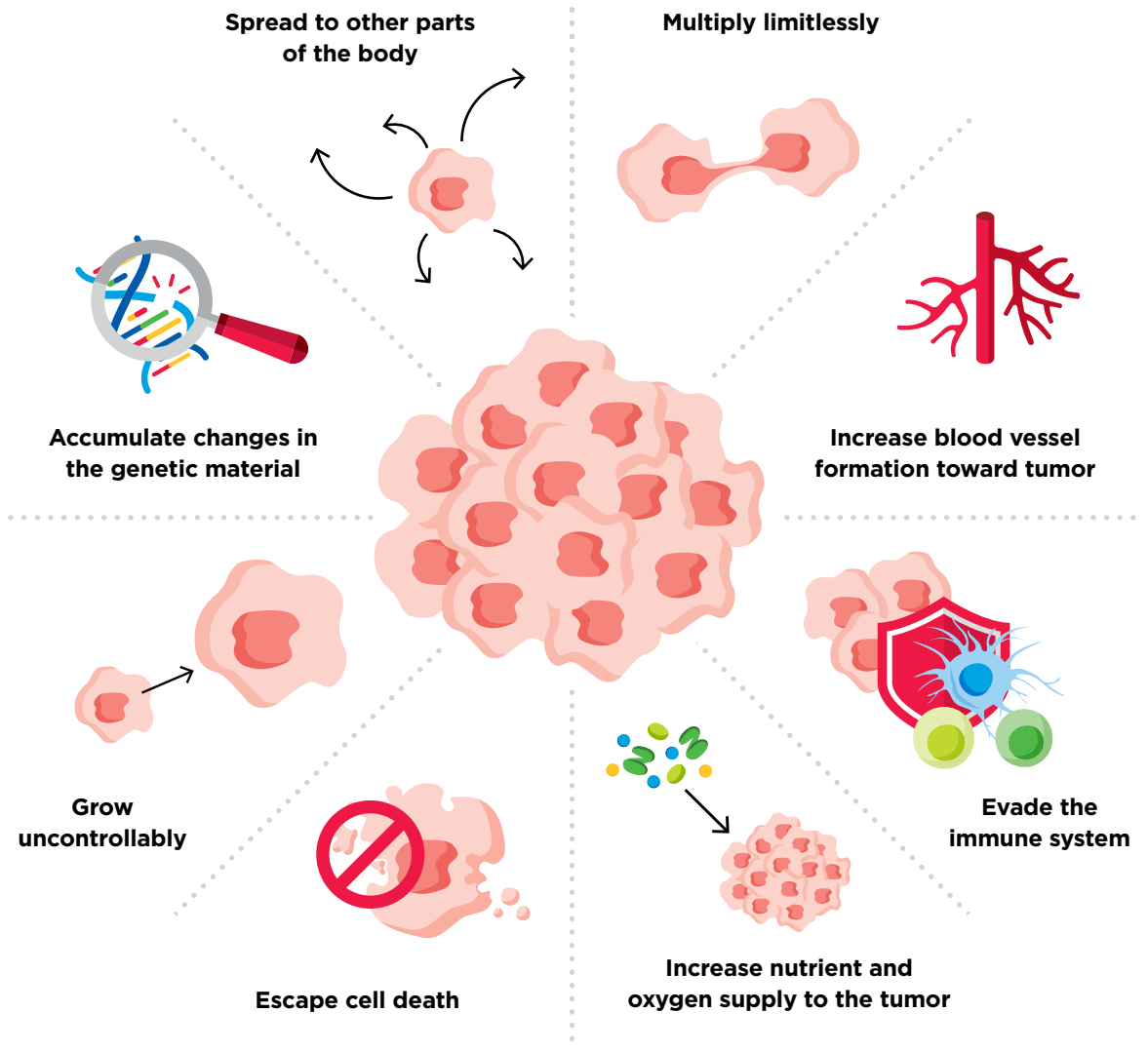
Cancer Development: Generating Knowledge

Basic research is focused on understanding living systems and life processes. For example, basic research plays an essential role in characterizing normal cell behavior and in identifying the alterations that drive cancer initiation and progression. The knowledge gained from basic research has provided the foundation for advances against cancer. Recognizing the critical role of basic research in improving the overall health for all individuals, more than 50 percent of the National Institutes of Health (NIH) budget has been allocated to basic research every year since 2003 (72).

Basic research plays a central role in the medical research cycle (see **Figure 5**, p. 28). Findings and hypotheses

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 the ability of cancer cells 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.

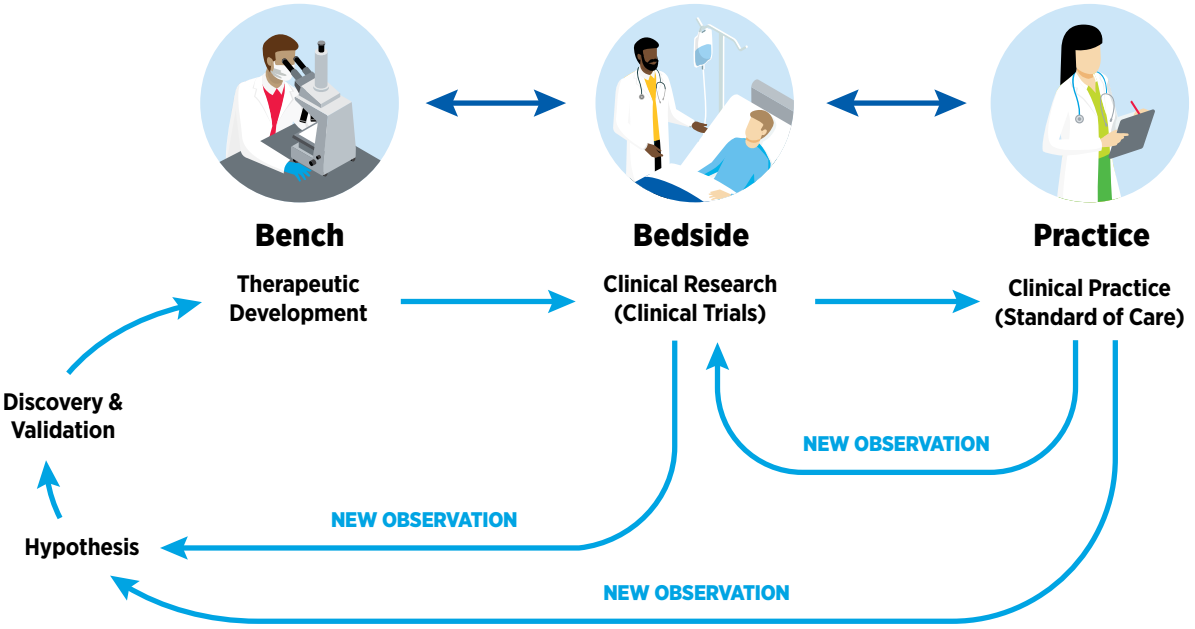
Source: (71).

stemming from the medical research cycle are fundamental to understanding what triggers cancer development; how cancer evades the body's defenses; and how cancer spreads within the body. This knowledge has led to improvements in the prevention of cancer, development of innovative imaging technologies, precise delivery of drugs to tumors, and selective and effective killing of cancer cells. Collectively, basic research-driven advances in cancer science and medicine are contributing to progress against cancer that is saving lives and improving health outcomes for countless patients.

Researchers working across the fields of medicine study the significance of a new discovery in a wide range of models that mimic healthy and diseased conditions (see **Sidebar 4**, p. 29). Findings from these studies can lead to the development of new anticancer drugs, innovative technologies, and

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 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 changes in public health policies and regulations.

Source: (73).

strategies for cancer screening and prevention, each of which has the potential to improve public health.

Basic Research: Vital for Making Progress Against Cancer

Decades of basic research, and discoveries stemming from it, have provided the foundation for progress against cancer. A prime example is the finding in the 1950s of a biochemical process called phosphorylation (74,75). The discovery of phosphorylation, the addition of phosphate groups to proteins and lipids, fundamentally changed the understanding of cellular regulation.

Phosphorylation is one of the most important modifications that modulate the activity of many proteins and lipids involved in cell division, growth, survival, and death. Research has shown that altered phosphorylation often leads to uncontrolled cell proliferation and survival, two major hallmarks of cancer (76).

Phosphorylation is a reversible process, which is mediated by specialized enzymes, called kinases and phosphatases. For example, in response to signals from outside the cell, protein kinases add phosphate groups to proteins and protein phosphatases remove them (77). Research has shown that alterations in kinases and phosphatases can lead to cancer development (78).

SIDEBAR 4

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 derived from different types of tumors that can be grown continuously in the laboratory.

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

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 destroy the patient's tumor in mice before they are given to the patient.

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

TISSUES are entire pieces of cancerous or healthy biospecimens obtained from humans or animals through biopsies or surgery.

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

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

Source: (29).

There are 518 protein kinases and 20 lipid kinases in human cells (79). Thanks to decades of research, mechanisms by which kinases add phosphate groups to proteins and lipids are well understood (77). Furthermore, kinases (as well as phosphatases) are frequently mutated in cancer, and many of these mutations contribute to the onset and progression of cancer (78). Knowledge gleaned from this research has established kinases as attractive drug targets for treatment of cancer (80). For example, imatinib (Gleevec), which was approved by the US Food and Drug Administration (FDA) in 2001 to treat chronic myelogenous leukemia, is the first molecularly targeted anticancer drug against a protein kinase (81). As of June 2024, there are 70 FDA-approved anticancer drugs targeting various kinases for the treatment of different types of cancer (82).

Another prominent example of the contributions of basic research to progress against cancer is the advent of modern immunotherapy, one of the most exciting new areas of cancer treatment. Groundbreaking basic research in the 1980s and 1990s uncovered the ways in which T cells function. T cells are immune cells that protect the body from infections and can also help fight cancer (see **Sidebar 36**, p. 107). Intriguingly, some tumor cells have increased levels of certain proteins on their surface that attach to and activate "brakes" on T cells, thus stopping them from attacking cancer cells. These brakes are proteins on the surface of T cells and are called immune checkpoint proteins. Immune checkpoint inhibitors (ICIs) are a class of transformative new therapeutics that can release the brakes on T cells and trigger T cells to destroy cancer cells (83). The first ICI, ipilimumab, was approved by FDA in 2011 to treat advanced-stage melanoma. Since then, FDA has approved 12 additional ICIs, and there is at least one ICI to treat more than 20 different types of cancer (see **Releasing the Brakes on the Immune System**, p. 107).

Cancer Development: Interpreting Knowledge

Cancer is a collection of diseases with the common feature of uncontrolled growth of cells. Often, there are genetic alterations to the instructions encoded in a cell's genetic material that disrupt tightly controlled functions, such as cell growth and division. Many of these changes are only the first step in a complex and multistep process that is influenced by changes both inside and outside the cell and that ultimately leads to the development of cancer.

Researchers use several ways to characterize cancers, depending on the type and purpose of the research and/

SIDEBAR 5

How Are Cancers and Tumors Characterized?

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

By site of origin

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

By tissue type

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

CARCINOMA	SARCOMA	MYELOMA	LEUKEMIA	LYMPHOMA
Begins in the skin or in tissues that line or cover internal organs.	Begins in bone or in the soft tissues of the body, such as fat or muscle.	Begins in plasma cells, a type of white blood cell that normally makes antibodies.	Begins in blood-forming tissue, such as the bone marrow.	Begins in cells of the immune system.

By grade

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

GRADE X	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Undetermined grade	**Low grade**	**Intermediate grade**	**High grade**	**High grade**
When a grade cannot be assessed.	When cells are well differentiated.	When cells are moderately differentiated.	When cells are poorly differentiated.	When cells are undifferentiated.

By spread

Classifies cancers based on the extent to which cancer has spread throughout the body. This approach to describe cancer is called the TNM staging system (where T refers to the primary tumor; N refers to the regional lymph node—a tissue in the lymphatic system; and M stands for metastasis—when the cancer has spread to parts of the body that are distant from the primary site of origin). A simplified description of cancer stages using this approach is described below:

PRECANCEROUS STAGE OR STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV
Also called *in situ* cancer, is a condition that may become cancer in the future if untreated.	Cancer that is localized to the tissue of origin.	Cancer that has spread to nearby lymph nodes or other tissues.	Cancer that has spread to nearby lymph nodes or other tissues to a greater extent than stage II.	Cancer that has metastasized to other parts of the body.

It is important to note that the classification of cancers increasingly includes biological and molecular features of cancer, thanks to research-driven knowledge of the genetic and epigenetic alterations in different cancer types. For example, breast cancer is further characterized by the presence or absence of certain proteins known as estrogen, progesterone, and HER2 receptors.

Source: (1).

or reporting (see **Sidebar 5**, p. 30). In most cases, several methods are simultaneously used to classify the type of cancer that a person has.

Changes That Contribute to Cancer Initiation

Deoxyribonucleic acid (DNA) constitutes the genetic material of cells and carries instructions for important cellular functions. DNA is a complex molecule that is made up of two strands, each of which is a string of four unique molecules called bases, designated A, T, C, and G. The two strands are paired together to form a double helix. The entirety of a person's DNA is called the genome. In humans, DNA resides inside the nucleus and is wrapped around proteins called histones. The packaged DNA is called chromatin and is further compacted into structures called chromosomes. Nearly all human cells have 46 chromosomes.

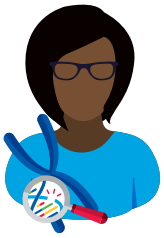
Each chromosome contains hundreds to thousands of genes. The cell uses a complex process, called transcription, to copy the instructions or messages that are embedded in genes to make messenger ribonucleic acid (mRNA) molecules. Another complex process, called translation, copies the information in mRNAs to make proteins, which are functional units of the cell. The amount of mRNA or protein produced is influenced by cellular needs. The following sections describe the types of changes within a cell that may 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 the amount of mRNA and the resulting protein, thus disrupting or modifying normal protein function and contributing to cancer development. Genetic alterations can be inherited (also called germline mutations) or acquired during a person's lifetime (also called somatic mutations) (see **Sidebar 6**, p. 32). Not all genetic alterations lead to cancer.

About 10 percent of cancer cases are caused by germline mutations. Germline mutations occur in a body's reproductive cells (egg or sperm) that are passed on from parents to children and become incorporated into the DNA of every cell in the body of the offspring. These types of mutations can increase their risk of developing cancer, although not all germline mutations contribute to cancer development. Inherited genetic alterations that play a role in cancer development are among the pathogenic germline mutations (see **Figure 6**, p. 33). However, even among pathogenic mutations, certain genetic alterations are more penetrant—meaning most people who carry the alteration will develop cancer—than others.

A recent study of breast cancer patients found that **germline mutations** in genes that drive breast cancer development, as well as in genes that help immune cells recognize cancer cells, **contribute to tumor progression and immune evasion**.



Source: (86).

W11

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 evaluating genome sequences of nearly 7,788 patients with lung cancer revealed that about 15 percent of the patients with lung cancer had well-described germline pathogenic mutations (85). Most of the mutations were found in genes needed for repairing damaged DNA, indicating these mutations may contribute to a person's predisposition to lung cancer (85).

Somatic or acquired mutations occur over an individual's lifetime due to errors arising during normal cell divisions or because of environmental exposures, lifestyle factors, and/or chronic health conditions. Research has revealed that different tumors can also contain different somatic mutations, depending on their site of origin.

Researchers are leveraging the understanding of genetic mutations present in cancer cells to treat cancer. In the past two decades, FDA has approved a number of targeted therapeutics based on genetic mutation(s) present in the cancer (87). Furthermore, genetic tests that identify germline mutations are helping to predict a person's risk of developing cancer, evaluate the risk of cancer in family members, and make informed and active decisions about their health.

RNA Variations

Most human genes contain interspersed sequences called exons and introns. Exons contain the instructions for making proteins, while introns do not contain the information necessary to make a functional protein. The mRNA molecule that is initially transcribed from a gene contains both exons and introns. A "cut and paste" process, called splicing, removes introns and then joins exons together to produce an mRNA molecule that is subsequently translated into a functional protein. RNA splicing is mediated by specialized proteins and is critical for normal cellular functions.

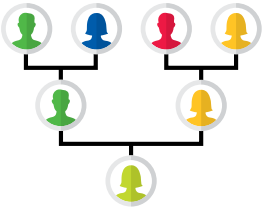
SIDEBAR 6

What Are Genetic Alterations?

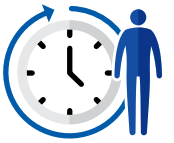
Genetic alterations include changes in the DNA sequence. While not all genetic alterations cause cancer, many result in downstream changes in the sequence or amount of mRNA and/or proteins produced that can drive or contribute to cancer development. Genetic alterations are one of the hallmarks of cancer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

Ways By Which Genetic Alterations Are Acquired:

BY INHERITANCE FROM PARENTS



DURING A PERSON'S LIFETIME FROM:



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

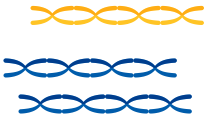
Types of Genetic Alterations That Contribute to Cancer Development

SINGLE BASE CHANGE

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

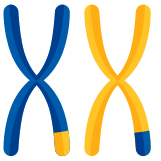
GENE AMPLIFICATION

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



STRUCTURAL GENETIC VARIATION

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



DELETION

Indicates loss of sections of genes or sections of chromosomes, which can result in loss of genes that are necessary to regulate processes that control normal cell growth, multiplication, and survival.

Adapted from (1).

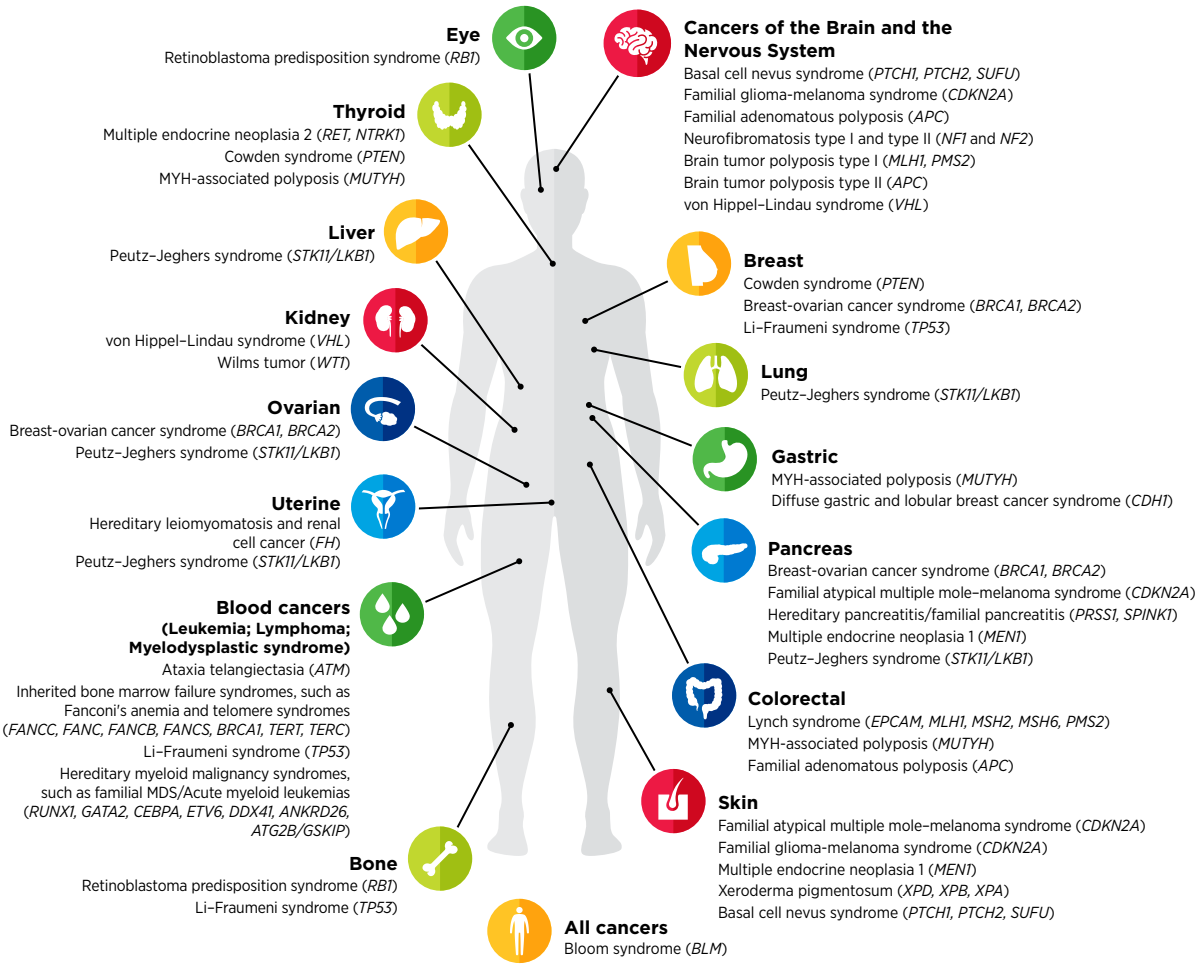
Changes in proteins that mediate splicing can produce aberrant mRNA molecules, which subsequently make abnormal proteins that can fuel cancer development, lead to treatment resistance, and alter immune cell function (88). Ongoing research is focused on understanding how cancer-related changes in RNA splicing can be leveraged for therapeutic purposes (89).

In addition to mRNA, cells also produce RNA molecules that are not translated into proteins. These RNA molecules are called noncoding RNAs (ncRNAs), and they play important roles in normal cell functions as well as in cancer cells (90). Two major types of ncRNAs produced in cells are microRNAs (miRs or miRNAs) and long noncoding RNAs (lncRNAs). miRs are about 17 to 25 bases long and largely function by binding to mRNAs and blocking their translation into proteins (91). lncRNAs are longer than 200 bases and regulate cellular functions in several ways, including functioning as signals for when a gene should be transcribed into mRNA, and guiding proteins to places within cells where they are needed (92).

ncRNAs can either function to promote cancer development or prevent normal cells from becoming cancerous (93,94). For example, miR-15 and miR-16, two well-studied miRs, inhibit cancer development by blocking the generation of proteins that help cancer cells grow as well as those that protect cancer cells from death (95). Loss of miR-15 and miR-16 promotes cancer cell growth and survival in several cancer types, including chronic lymphocytic leukemia, prostate cancer, and multiple myeloma (95). Similarly, HOTAIR, a well-studied lncRNA, is linked with multiple cancer types, including breast cancer,

FIGURE 6

Inherited Cancer Risk



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

Source: (84).

colorectal cancer, and glioma (96). In colorectal cancer, the more HOTAIR cancer cells have, the more they become resistant to treatment, leading to poor outcomes (97).

Research has shown that transcriptomics—the study of all RNA molecules in a cell—can help differentiate the types and levels of RNA that are present in healthy versus tumor tissues. Such information can reveal how different types of RNA contribute to cancer development and may identify RNA molecules that can be used to predict progression of cancer and response to treatment. Thanks to technological advances in RNA sequencing, researchers can now determine transcriptomes of single cells within a tumor. The in-depth knowledge gained from such studies is uncovering new mechanisms by which cancer develops, progresses, spreads to distant sites, and/or becomes resistant to treatment (98,99).

Protein Modifications

The complete set of proteins made by human cells is called the proteome and contains about 20,000 unique proteins. The proteome of cancer cells has revealed important information about cancer that may not have been apparent from genomic or transcriptomic analyses. As one example, bladder cancer is highly heterogeneous, and it is not easy to predict treatment response based on genomic and transcriptomic analyses alone. In a recent

study, researchers evaluated the proteome from 242 tumors isolated from patients with bladder cancer and identified protein modifications that predict response to the treatment with higher accuracy (100). Further analysis suggested that some of the investigational anticancer drugs not currently in clinical use may be more effective in treating patients with bladder cancer (100), indicating that studying the proteome can inform new treatment options.

The functions of many proteins are controlled by posttranslational modifications (PTMs), which are characterized by reversible addition and removal of molecules, such as phosphate (see **Basic Research: Vital for Making Progress Against Cancer**, p. 28). Proteins undergo PTMs depending upon cellular needs and they are necessary for normal cellular functions, such as responding to signals from outside the cell (101). Researchers estimate that there are more than 400 different types of PTMs that modulate various aspects of protein functions (102). Changes in normal PTMs of proteins can contribute to cancer (102). In a recent study, researchers analyzed PTM profiles from 1,110 patients across 11 cancer types (103). Findings of the study revealed that different types of PTMs are associated with different hallmarks of cancer. For example, the researchers found that altered phosphorylation was associated with tumors in which machinery to repair DNA was defective, while altered acetylation, another type of PTM, was more prevalent in tumors with altered metabolism (103).

Epigenetic Changes

Epigenetic modifications change the structure of DNA without altering the DNA sequence. These changes involve the addition or removal of chemical marks on DNA or the PTMs of histones, which are the proteins that package DNA into chromosomes. Specialized proteins facilitate the addition or removal of these unique modifications on DNA and histones (104). Epigenetic alterations are influenced by aging, environmental exposures (e.g., air pollution), behavioral risk factors (e.g., smoking), and chronic stress (e.g., systemic racism). Furthermore, these modifications are heritable and can contribute to a person's risk of developing cancer.

Epigenetic modifications determine when and how genes are activated or silenced. For example, depending on cellular needs and in response to signals from outside the cell, epigenetic changes can make genes accessible to the machinery that makes mRNA. Unlike genetic mutations, epigenetic changes are typically reversible.

The entirety of epigenetic changes within a cell is called the epigenome. Research has significantly advanced our understanding of how the epigenome is modified in cancer and how these changes contribute to cancer (105). The reversible nature of epigenetic modifications has made them compelling targets for drug development. Consequently, several anticancer drugs that modify the cancer epigenome have been developed and approved by FDA (105).

Understanding of the epigenome and the proteins that regulate it is being used to further comprehend cancer development at a molecular level (106). For instance, in a recent study, researchers evaluated the role of the epigenome at various steps during cancer development across 11 cancer types (107). Findings of the study showed that unique sets of proteins that regulate the epigenome are associated with the onset of cancer, how cancer progresses, and how it metastasizes (107). These discoveries are paving the way for identifying new therapeutic targets and accelerating the development of new drugs to treat cancer.

Systems That Enable Cancer Progression

A hallmark of cancer is the ability of tumor cells to break away from the primary tissue and travel to other parts of the body. Systems that enable cancer to spread from the primary tissue site to other organs of the body include the blood system, the lymphatic system, and the immune system (see **Sidebar 7**, p. 35).

The Blood System

Angiogenesis is the formation of new blood vessels, which occurs throughout 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, and whose functions are hijacked by cancer cells to increase tumor angiogenesis (108). For example, vascular epidermal 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 (109).

Over the past two decades, several drugs that block angiogenesis have been approved to treat cancer. In 2004, FDA approved the first anti-angiogenic drug bevacizumab (Avastin), which blocks VEGF. Since then, FDA has approved 12 different anticancer therapeutics targeting proteins that promote angiogenesis, to treat 13 different cancer types (see **Figure 17**, p. 97) (73).

The Lymphatic System

The lymphatic system consists of an extensive network of vessels, called lymph vessels or lymphatic vessels; small bean-

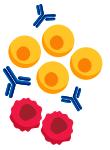
SIDEBAR 7

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.

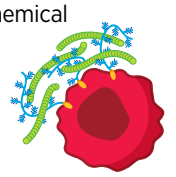


TUMOR MICROENVIRONMENT-ASSOCIATED CELLS that are not immune cells, such as pericytes, endothelial cells, fibroblasts, and astrocytes, that can also support tumor growth by stimulating tumor cell multiplication, triggering formation of new blood vessels, and enhancing survival of cancer cells.

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

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



Source: (1).

shaped structures, called lymph nodes; and other organs such as the spleen, thymus, tonsils, and adenoids. The lymphatic system maintains total body fluid levels, removes cellular waste from tissues, detects pathogens, absorbs fats, and produces immune cells and antibodies in the lymph nodes.

One of the ways cancer cells travel to other parts of the body is through the lymphatic system. When spreading to other body parts through the lymphatic system, cancer cells can accumulate in one or more of the nearest lymph nodes. The presence of cancer cells in lymph nodes is one of the ways to determine the stage and/or the extent of cancer (see **Sidebar 5**, p. 30).

Cancer cells shed by the tumor release certain molecules that help them move toward the lymphatic system. In addition, cancer cells adopt mechanical changes that facilitate their entry into the lymphatic system (110). Once inside the lymphatic system, cancer cells acquire additional properties that make them more aggressive and facilitate their spread to other parts of the body (111).

Researchers are working on ways to leverage the lymphatic system for targeted delivery of anticancer therapy to lymph nodes where cancer cells can accumulate. Furthermore, ongoing work is focused on developing drugs that can prevent cancer cells from reaching and entering the lymphatic system (110).

The Immune System

The immune system helps the body fight infections and other diseases, including cancer. Multiple cell types, tissues, and organs make up the immune system and they work in concert to detect and remove pathogens as well as abnormal or damaged cells from the body. There are two main components of the immune system. The innate immune system is the body's first line of defense that provides a general, nonspecific response to pathogens. It includes physical barriers like 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 the future. This includes B cells that produce antibodies to neutralize pathogens, as well as T cells that can kill infected cells and/or help coordinate other immune responses (see **Sidebar 36**, p. 107).

The immune system constantly monitors the body for the presence of abnormal or damaged cells, including cancer cells, in a process called cancer immune surveillance (112). However, as cancer progresses, some cancer cells obtain properties that help them evade the immune system. Research has revealed several ways cancer cells evade the

immune system (113). In some cases, cancer cells disrupt the cellular machinery that helps immune cells recognize damaged or abnormal cells. In others, cancer cells exhibit increased levels of proteins that function as brakes on the immune system. And in yet other cases, cancer cells release molecules that prevent the immune cells from becoming fully functional (114). Increasing evidence also suggests that certain immune cells present in the tumor microenvironment promote tumor growth (115).

The Microbiome

All microorganisms (e.g., bacteria and fungi) and viruses that live in the gut, skin, and mouth, and other sites in the body, collectively make up the human microbiome. Research has shown that the microbiome plays a critical role in health outcomes (116-118).

Most of the microorganisms in the human microbiome are beneficial to health, but some are potentially harmful. Accumulating evidence suggests that the balance between helpful and potentially harmful microorganisms in the gut microbiome contributes to overall health, while an imbalance contributes to a number of diseases, including cancer (119). In cancer, the microbiome can influence progression and spread of the disease through interactions among microorganisms, between the microbiome and the patient's immune system, and through secretion of molecules (120,121). Furthermore, microorganisms living in different parts of the body can be associated with specific cancer types. For example, research has shown that specific types of bacteria present in the mouth are prevalent in patients with oral cancer. Conversely, an abundance of another type of bacteria is correlated with better overall survival in patients with oral cancer (122). As another example, the interplay between the vaginal microbiome and human papillomavirus (HPV) in cervical precancers and cancer development is an area of ongoing research (123,124).

Research has shown that the microbiome can inform response to treatments and predict health outcomes (125). For example, a recent study analyzing microbiomes of more than 4,000 tumors showed that a specific type of bacteria was associated with resistance to immune checkpoint inhibitor treatment in patients with lung cancer (126). These findings and those from similar studies suggest that modulating the microbiome can boost the effectiveness of certain anticancer treatments such as immunotherapies (127).

It is clear that targeting the microbiome may help improve health outcomes for patients with cancer. Researchers are actively working to address many outstanding questions, such as the interplay between the microbiome and the host before such interventions can become a part of routine clinical care (128,129).

Processes That Promote Cancer Growth and Metastasis

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

According to the most recent estimates available, there were 623,405 people living with metastatic breast, prostate, lung, colorectal, or bladder cancer or metastatic melanoma in the United States in 2018, and that number is expected to increase to 693,452 by 2025 (10). The 5-year survival rates are significantly lower in patients with metastatic cancer compared to those with localized cancer (2). Although the causes of death in patients with cancer are complex and multifaceted, patients with metastatic disease are significantly more likely to die compared to those whose cancer has not metastasized (130). Furthermore, chances of a cure are limited in patients with metastatic cancer. Complex processes facilitate cancer metastasis and finding additional ways to effectively treat patients with advanced stage disease are active areas of research.

Tumor Evolution and Heterogeneity

Tumors are highly heterogeneous where (i) the cancer cells within them have distinct alterations and features within a tumor; (ii) there can be significant differences between tumors of the same type in different patients; and (iii) there are major differences between a primary (original) tumor and the metastatic tumor. Tumor heterogeneity arises from acquisition of new alterations in the genomes, epigenomes, transcriptomes, and proteomes of cancer cells as they divide. Over time, these changes accumulate and contribute to the genetic diversity of cancer cells within the tumor. Furthermore, the tumor microenvironment can influence cancer cell behavior, leading to distinct subpopulations of cancer cells within the same tumor. Collectively the process by which tumors acquire heterogeneity is called tumor evolution (131-133). The heterogeneity of cancer cells in the tumor enables some cancer cells to acquire properties that facilitate their spread to other parts of the body. Tumor heterogeneity also poses significant challenges for cancer treatment. The presence of diverse subpopulations of cancer cells within a tumor can lead to differential responses to therapy, with some subpopulations being more resistant to treatment than others. This can result in treatment failure and disease recurrence (134) (see **Sidebar 31**, p. 95).

Two recent studies using advanced techniques have developed a comprehensive three-dimensional map of glioma, which revealed interesting details of tumor heterogeneity in this deadly type of brain cancer that has no effective treatment available (135,136). In one study, researchers combined a precision surgical procedure with single cell genomic, transcriptomic, and epigenomic analyses to identify molecular pathways that contribute to the heterogeneity of glioblastoma multiforme, a type of glioma (135). The second study found that gliomas are composed of subpopulations of cells that share similar molecular traits and that certain subpopulations always exist in proximity to each other. Researchers found that low oxygen conditions, a hallmark of cancer, play a significant role in this complex organization (136). Similar analyses are being performed for many cancers, including other aggressive and difficult-to-treat diseases, such as certain types of skin cancer (137), pancreatic cancer (138), small cell lung cancer (139), and certain types of breast cancer (140).

In-depth understanding of tumor heterogeneity helps develop treatment strategies that are more effective. For example, using combinations of drugs that target different characteristics of a tumor can help overcome treatment resistance. Furthermore, the cellular and molecular profile of a patient's tumor can help develop personalized treatment plans that are more likely to be effective.

Epithelial-to-mesenchymal Transition

Epithelial-to-mesenchymal cell transition, or EMT, is an essential developmental process (141). Epithelial cells are tightly connected with each other and form the covering of all body surfaces, line body cavities and hollow organs, and are the major tissue in glands. In EMT, epithelial cells acquire the properties of another type of cell called mesenchymal cells, which form the connective tissue, blood vessels, and lymphatic tissue and have the ability to migrate within the body. This transition allows epithelial cells to move within the embryo during the formation of organs (141). EMT is also essential for wound healing and tissue regeneration throughout life (142).

Roughly 90 percent of cancers develop in epithelial cells (143). Cancers that develop in epithelial cells hijack pathways fundamental for EMT. This hijacking of EMT pathways by cancer cells is one of the hallmarks of cancer and plays a central role in metastasis (144). Research has established that EMT is regulated by several proteins that promote cancer cell division, survival, and mobility, and enable metastasis (145,146). Recent studies have found that EMT also plays a critical role in the ability of cancer cells to evade the immune system (147).

Ongoing research is exploring whether therapeutically targeting proteins involved in EMT could improve clinical outcomes. For example, findings from two recent studies show that the levels of netrin-1, a protein that is normally present during embryonic development and is involved in blood vessel formation, cell survival, and brain development, are increased in cancer cells undergoing EMT (148,149). Researchers found that blocking the activity of netrin-1 not only blocked EMT but also inhibited tumor growth in endometrial cancer (149) and skin cancer (148).

Tumor Microenvironment

Cancer cells interact with and alter their surrounding cells and tissues to maintain their uncontrolled growth, accumulate within their primary site, and spread to other organs. The combination of cells, molecules, and blood vessels that support and sustain cancer cells is known as the tumor microenvironment. This environment plays a crucial role in influencing tumor growth and metastasis, while cancer cells, in turn, can modify the tumor microenvironment to enhance their survival and proliferation.

Cancer cells secrete molecules that modify their surroundings to ensure an adequate supply of nutrients and oxygen and to provide structural support (see **Sidebar 7**, p. 35). Furthermore, the tumor microenvironment can adapt in ways that impede the effectiveness of immune cells or anticancer drugs, making it more difficult to target and destroy tumor cells (150,151).

The importance of the tumor microenvironment in cancer initiation, progression, metastasis, and as a barrier to treatment, has made it a significant focus for therapeutic development. Researchers are exploring ways to modify immune cells to enable them to penetrate the tumor microenvironment and effectively kill cancer cells (152). One such approach involves isolating T cells from within a patient's tumors, expanding them in the laboratory, and injecting them back into the patient. Because these T cells have already acquired the properties that enable them to infiltrate the tumor, they can overcome barriers posed by the tumor microenvironment effectively. The potential of this approach is underscored by FDA approval in February 2024 of the first such therapeutic (see **Boosting the Cancer-killing Power of Immune Cells**, p. 112) (153). Additionally, therapies aimed at inhibiting tumor angiogenesis—thereby cutting off the tumor's supply of oxygen and nutrients—have shown considerable promise in targeting the tumor microenvironment and impeding tumor growth (152).

★ SPOTLIGHT

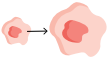
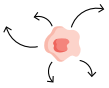
Understanding the Biology of Childhood Cancers

Research over the past two decades has uncovered the molecular underpinnings of childhood cancer and has revealed features that distinguish childhood cancers from

★ SIDEBAR 8

Key Differences in Hallmarks of Cancer Cells Between Childhood and Adult Cancers

Research over the past two decades has revealed key differences in hallmarks of cancer between pediatric and adult cancers. Some of these differences are highlighted below:

Hallmark of Cancer	Childhood Cancers	Adult Cancers
 **GENETIC MUTATIONS**	Fewer mutations, and more often in genes involved in embryonic development, such as transcription factors and chromatin regulators	More mutations, frequently in genes involved in key cellular pathways
 **GENOMIC INSTABILITY**	Less genomic instability, driven by specific chromosomal translocations	High genomic instability driven by genetic mutations accumulated over time
 **UNRESTRICTED GROWTH**	Driven by signals that control development	Driven by signals that control cell division and growth
 **EVADING CELL DEATH**	Often depends on activation of survival pathways involved in embryonic development	Often depends on inactivation of pathways that direct cell death
 **METASTASIS**	Often occurs through pathways involved in embryonic development	Occurs largely through epithelial-to-mesenchymal transition
 **ALTERED METABOLISM**	Metabolic changes resemble embryonic developmental states of rapid multiplication	Metabolic changes include altered lipid, sugar and amino acid metabolism

Source: (71,158,159).

adult cancers (see **Sidebar 8**, p. 38). At the molecular level, there is an increasing recognition that germline mutations play a pivotal role in childhood cancer, with studies indicating that at least 10 percent to 15 percent of childhood cancers are driven by germline mutations (154-156). Furthermore, structural alterations in DNA, such as chromosomal rearrangements and chromosomal translocations, play a central role in the initiation and progression of childhood cancers.

IN A RECENT STUDY OF CHILDHOOD CANCERS **50% OF THE CANCERS CARRIED A GENETIC ALTERATION THAT CAN** BE USED AS A POTENTIAL DRUG TARGET.

Source: (157).

W12

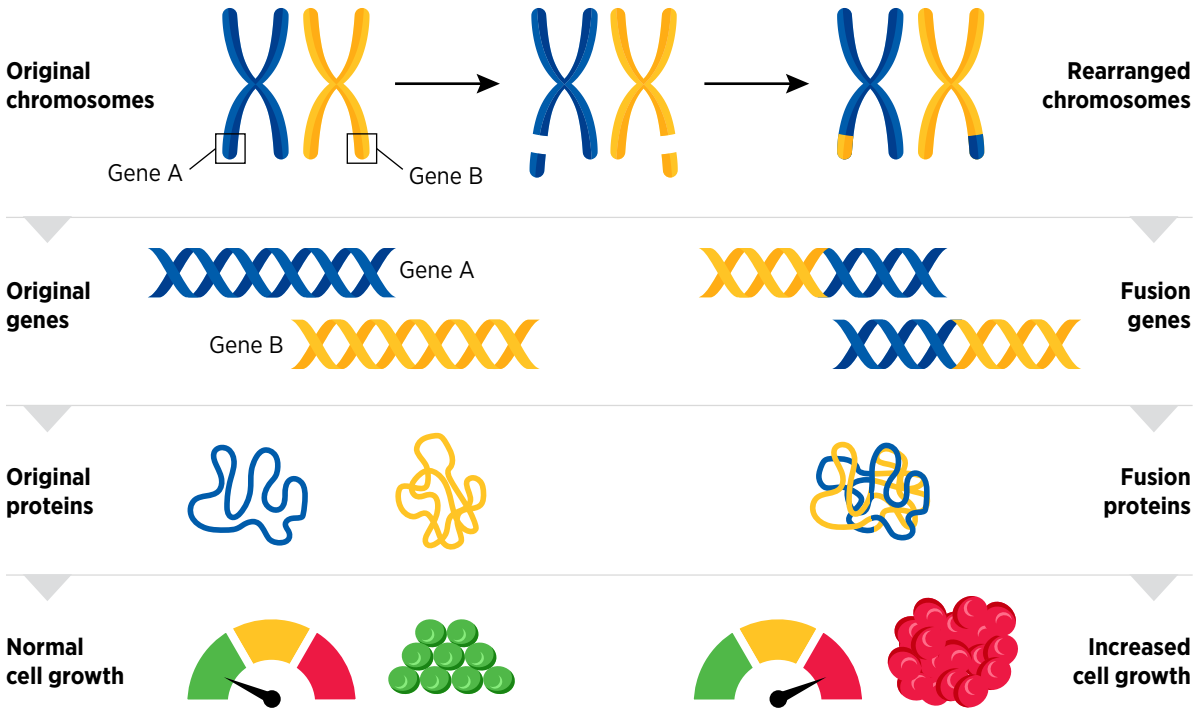
Chromosomal Rearrangements in Childhood Cancers

Chromosomal rearrangements are structural variations in which two genes, present on two different chromosomes (more common) or on the same chromosome (less common), fuse together to make a fusion gene that is not present in normal cells. This rearrangement not only disrupts functions of the proteins encoded by genes involved in chromosomal translocations, but also produces an entirely new protein from the fusion gene that can drive cancer initiation and progression (see **Figure 7**, p. 39).

Chromosomal rearrangements occur due to errors during cell division. For example, breaks in the DNA strands during cell division can lead to incorrect repair

★ FIGURE 7

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 the fusion genes often hijack and deregulate normal cellular mechanisms, such as cell growth, to drive cancer development.

and fusion of pieces of chromosomes. Chromosome breaks leading to fusion proteins are very common in childhood cancers and have been identified in many leukemias, solid tumors, and brain cancers in children (see **Table 2**, p. 40). Findings from a large study evaluating transcriptomic sequencing data from 5,190 children with cancer identified 272 fusion genes. Researchers also discovered multiple mechanisms by which these fusion genes can lead to cancer in children, including disrupted gene regulation and altered RNA splicing (see **RNA Variations**, p. 31) (160).

Understanding chromosomal rearrangements and their impact on cellular pathways is crucial for the diagnosis and treatment of childhood cancers. Targeted therapies that specifically address these molecular alterations have the potential to improve treatment outcomes and reduce adverse effects associated with chemotherapy or radiotherapy.

The Promise of Precision Medicine for Childhood Cancers

Precision medicine, or personalized medicine, means that patient treatment is based on characteristics that distinguish them from other individuals with the same disease (see **Cancer Development: Integrating Knowledge**, p. 41). Precision medicine has shown great promise in treating childhood cancers, as underscored by NCI's precision medicine initiatives focused on childhood cancer (see **Sidebar 9**, p. 41).

One example of how precision medicine is accelerating the pace of progress against childhood cancers is the use of new strategies to assess the risk status in medulloblastoma, the most common childhood brain tumor (163). Historically, the risk stratification of medulloblastoma tumors was assessed by the morphology of the cancer cells and how much surgical

★ TABLE 2

Most Common Chromosomal Rearrangements in Childhood Cancers

GENE A	GENE B	FUSION PROTEIN	CANCER TYPE	DISRUPTED PATHWAY
MYC on Chromosome 8	*IGH* on Chromosome 14	MYC-IGH	Burkitt Lymphoma	Transcription Regulation
PML on Chromosome 15	*RARA* on Chromosome 17	PML-RARA	Acute Promyelocytic Leukemia	Transcription Regulation
ETV6 on Chromosome 12	*RUNX1* on Chromosome 21	ETV6-RUNX1	Acute Lymphoblastic Leukemia	Transcription Regulation
PAX3 on Chromosome 2	*FOXO1* on Chromosome 13	PAX3-FOXO1	Alveolar Rhabdomyosarcoma	Transcription Regulation
EWSR1 on Chromosome 11	*FLI1* on Chromosome 22	EWSR1-FLI1	Ewing Sarcoma	Transcription Regulation
KMT2A on chromosome 11	Multiple genes on different chromosomes (e.g., *MLLT3* on chromosome 9)	Multiple fusion proteins (e.g., MLLT3-KMT2A)	Acute myeloid leukemia	Epigenetic regulation
RUNX1 on chromosome 21	*RUNX1T1* on chromosome 8	RUNX1-RUNX1T1	Acute myeloid leukemia	Transcriptional regulation
EWSR1 on chromosome 11	*WT1* on chromosome 11	EWSR1-WT1	Desmoplastic small round cell tumors	Transcription regulation
SS18 on chromosome 18	*SSX* on X chromosome	SS18-SSX	Synovial sarcoma	Epigenetic regulation
ZFTA on chromosome 11	*RELA* on chromosome 11	ZFTA-RELA	Ependymoma	Transcription regulation
BRAF on chromosome 7	Multiple genes on different chromosomes (e.g., *KIAA 1549* on chromosome 7)	Multiple fusion proteins (e.g., BRAF-KIAA 1549)	Pediatric low grade glioma	Cell signaling

Source: (161).

removal of the tumor was performed. The integration of epigenomics, such as DNA methylation profiles, has led to the identification of distinct molecular subtypes of the disease, and has significantly improved the decision-making for treatment, such as using less intense treatments for children with cancer who have more favorable molecular characteristics. Because of its impact on improving health outcomes for patients, molecular profiles are now a part of the World Health Organization's classification and risk assessment for the disease (164).

Another example of how precision medicine is improving outcomes for children with cancer is the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program. Using gene expression analyses, researchers confirmed that some children with acute lymphoblastic leukemia (ALL) have the *BCR-ABL* fusion gene, also called the Philadelphia chromosome, which was originally identified by imaging and other approaches. Additional analyses revealed that children with this genetic alteration have poor outcomes, leading to clinical trials evaluating the efficacy of molecularly targeted therapeutics that block the activity of the BCR-ABL fusion protein (165). Other advances in the development of molecularly targeted therapy through genomics are highly effective therapeutics being used in the clinic to treat TRK fusion-positive cancers, ALK fusion-positive cancers, and ALK-driven neuroblastoma (158).

★ SIDEBAR 9

The National Cancer Institute's Precision Medicine Initiatives

Childhood Cancer Data Initiative (CCDI)

Launched in 2019, CCDI aims to:

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

Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium

- FusOnC2, a part of Cancer Moonshot initiative, is a collaborative research effort to advance the understanding of the contributions of fusion proteins to the development of childhood cancers and inform the development of targeted treatments for pediatric patients.
- FusOnC2 brings together researchers with expertise in structural biology, proteomics, genomics, medicinal chemistry, pharmacology, and cancer biology.
- FusOnC2 researchers have already made major contributions to understanding molecular underpinnings of childhood cancers, such as Ewing sarcoma, that have been challenging to therapeutically target. For example, one study from the consortium showed that targeting TRIM8, a protein that regulates levels of the EWSR1/FLI1 fusion protein in Ewing sarcoma, can cause cancer cells to "overdose" on EWSR1/FLI1 and die (162).

Molecular Characterization Initiative (MCI)

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

NCI–COG Pediatric MATCH Trial

- The National Cancer Institute (NCI)–Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) is a precision medicine clinical trial for children, adolescents, and young adults, ages 1 to 21 years, taking place at about 200 children's hospitals across the nation.
- The NCI–COG MATCH trial tests the use of precision medicine for childhood cancers in young people with solid tumors who are not responding to standard treatment based on the genetic changes found in their tumors.
- As of January 31, 2024, the NCI–COG MATCH trial has recruited 1,371 participants for 13 different treatments.

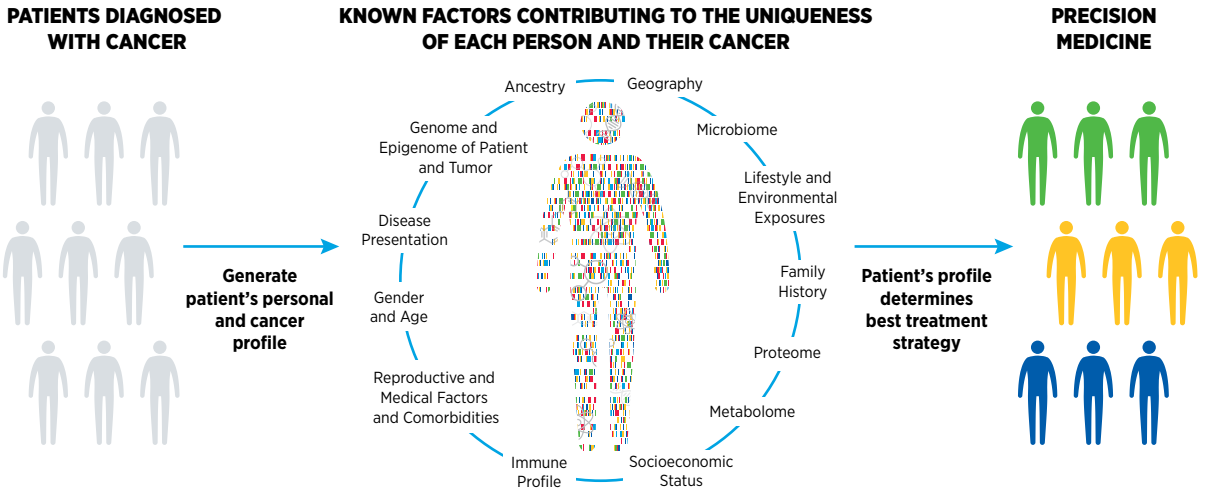
Cancer Development: Integrating Knowledge

Breakthrough discoveries and technological innovations have significantly advanced the understanding of cancer initiation and progression, enabling the development of a myriad of effective anticancer therapies in recent years. A crucial insight stemming from this knowledge is the understanding that each patient's cancer is unique at the molecular level. 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 8**, p. 42). For patients with cancer, precision medicine means using molecular characteristics of the tumor, such as the genome sequence of cancer cells, to make a diagnosis, plan treatment, evaluate whether treatment is working, and/or predict outcome.

In recent years, FDA has approved a number of anticancer therapeutics that are developed on the basis of genetic alterations that drive the characteristics of cancers, and many molecularly targeted drugs are being used to treat cancers that originate from different organs but share similar genetic characteristics (166,167). Furthermore, researchers are leveraging the ever-increasing information about a patient's tumors to develop effective treatment plans for patients with cancer who develop resistance to available treatment options. For example, although many molecularly targeted therapies and immunotherapeutics are available for the treatment of non–small cell lung cancer (NSCLC), patients eventually develop resistance to these treatments and experience adverse health outcomes. One of the ways tumors become resistant to the treatment with precision therapeutics is by mutations in proteins that help cells repair damaged DNA. Based on this knowledge, researchers used a combination of an immunotherapeutic and a molecularly targeted therapeutic developed against the mutated form of protein involved in

FIGURE 8

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.

DNA repair. Results show that the treatment combination significantly improved the overall survival in patients harboring the mutated form of protein involved in DNA repair to 22.8 months from 8.4 months with standard of care treatment (168).

The exciting new frontier of precision medicine is integrating all the information of a patient's tumor gleaned from analyzing the genome, epigenome, proteome, transcriptome, microbiome, and immune system, among other aspects, to develop a personalized treatment plan. In fact, researchers are already integrating multiple aspects of a patient's tumor to improve cancer diagnosis; identify precise drug targets; and predict treatment responses and outcomes more accurately (169).

Precision medicine holds immense promise to deliver better outcomes with reduced toxicity for patients with cancer. However, many questions remain unanswered, such as the cost-effectiveness of multidimensional profiling that is a prerequisite for personalized treatments and the extent to which such profiling improves outcomes for individuals (170). It is vital that stakeholders across cancer science, medicine, and public health work together to ensure that all patients with cancer can equitably benefit from breakthroughs being made in cancer care by precision medicine approaches (171).

Reducing the Risk of Cancer Development

IN THIS SECTION, YOU WILL LEARN:

- In the United States, 40 percent of all cancers are associated with modifiable risk factors, 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 cervical cancer, vulvar cancers, and penile or anus cancers caused by HPV.
- 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 cancers. 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 cancers.

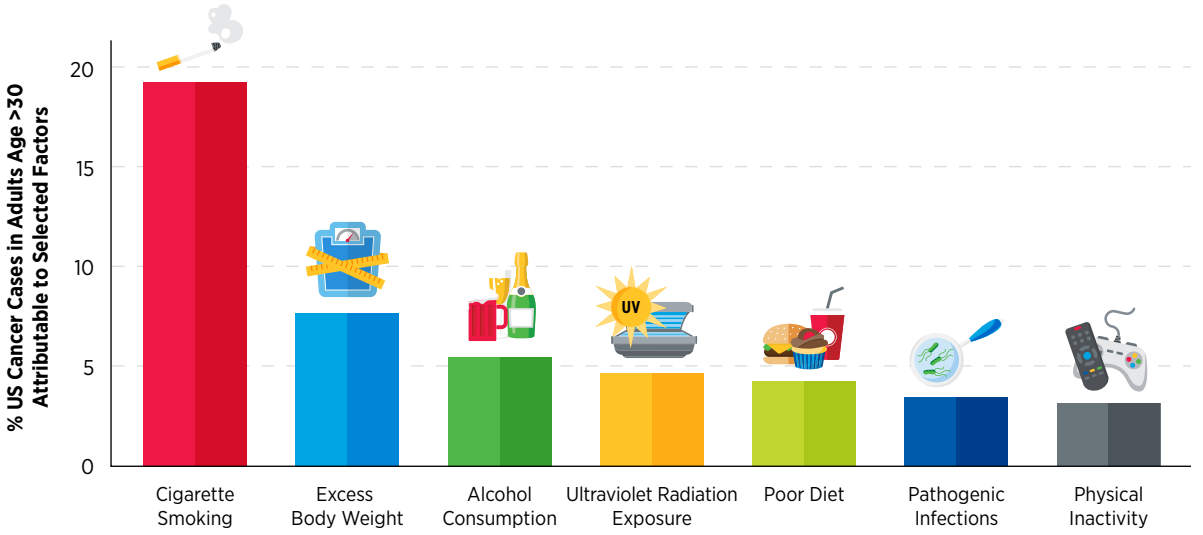
Research in basic, translational, and population sciences has broadened our understanding of the factors that increase an individual's risk of developing cancer (see **Figure 9**, p. 44). Modifiable risk factors, including tobacco use, unhealthy diet, physical inactivity, ultraviolet (UV) exposure, excessive alcohol consumption, pathogenic infections, and obesity, contribute to the development of 40 percent of all cancers (48). Given that several of these risks can be avoided or reduced, many cases of cancer can potentially be prevented.

In the United States, the age-adjusted overall cancer death rate declined by 33 percent between 1991 and 2021. This reduction is attributable in part to public health interventions as well as policy initiatives that reduced smoking and removed barriers to cancer screening, such as by reducing or eliminating co-payments for mammograms (4,172). However, while smoking rates have declined significantly, the increasing prevalence of other risk factors, including obesity among US children and adults, is a cause for public health concern. Additionally, there is a lack of widespread utilization in the United States of preventive interventions such as vaccination against cancer-causing viruses including human papillomavirus (HPV), which is the primary cause of cervical cancer.

Air pollution, water contamination, carcinogenic chemicals in consumable goods (e.g., cars and furniture), endocrine-

FIGURE 9

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.

Source: (1,48).

disrupting chemicals, and naturally occurring radon gas increase a person's risk for certain types of cancer, including common cancers such as lung cancer. While most individuals are exposed to these pollutants to some extent, some populations, such as those who live in low-income communities and rural areas, or on tribal lands, may be exposed to higher levels (30,173-177). Occupational exposures—any type of physical, chemical, or biological agents encountered in a person's employment that would increase the risk of injury or disease—such as to hazardous materials encountered during firefighting, silica dust in mines, and noxious fumes in fabrication and roofing can also increase a person's risk for developing cancer.

Emerging data indicate that certain cancer risk factors are also associated with worse outcomes after a cancer diagnosis, including development of secondary cancers. 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

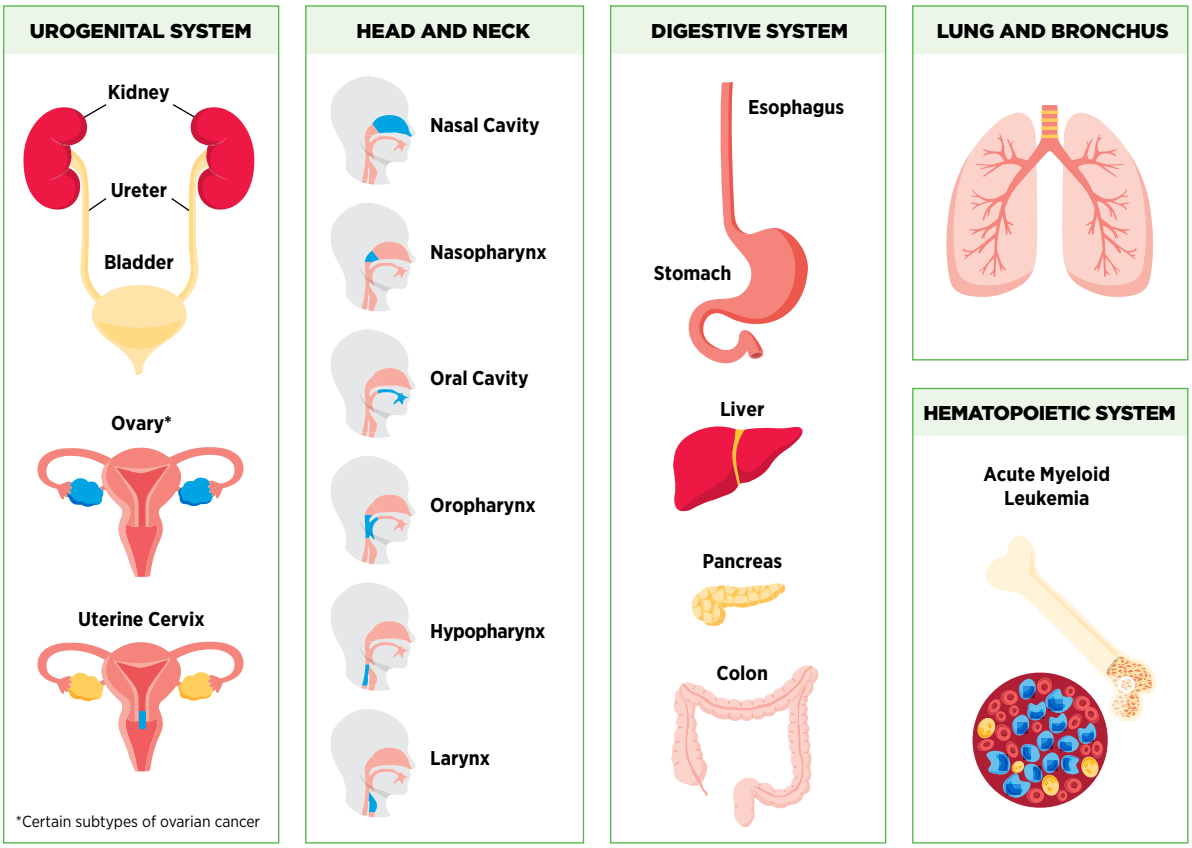
The use of tobacco products is the leading preventable cause of cancer and is associated with the development of 17 different types of cancer in addition to lung cancer (see **Figure 10**, p. 45). Nearly 20 percent of all cancer cases and almost 30 percent of all cancer-related deaths are caused by smoking cigarettes (48). In the United States, between 80 percent and 90 percent of lung cancer deaths are attributable to smoking (178). On average, people who smoke die 10 years younger than those who have never smoked (179).

Research over the past 50 years has consistently demonstrated that byproducts released from smoking tobacco products, such as cigarettes, cause permanent cellular and molecular alterations, which lead to cancer (180-182). Furthermore, smoking causes many other chronic conditions, including chronic obstructive pulmonary disease (COPD), asthma, and many types of cardiovascular diseases, particularly coronary artery disease.

Thanks to nationwide tobacco control initiatives, cigarette smoking among US adults has been declining. In fact, cigarette smoking rates among US adults have decreased

FIGURE 10

Beyond the Lungs: Cancers Caused by Smoking Tobacco



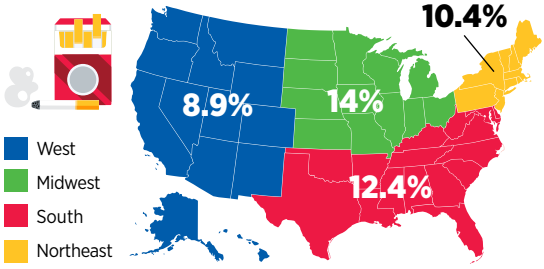
Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer. No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke. Use of smokeless tobacco (such as chewing tobacco and snuff) can cause oral, esophageal, and pancreatic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

Source: (1,48).

from 42.4 percent in 1965 to 11.5 percent in 2021 (49). However, even in 2021, the most recent year for which such data are available, an estimated 46 million US adults reported using any tobacco product (e.g., cigarettes, cigars, pipes) (49). In the United States there are geographical differences in smoking rates, which has led to certain regions with high smoking prevalence being associated with higher rates of lung cancer mortality (183).

There are striking sociodemographic 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 tobacco use is higher among US residents who live in rural areas and in the Midwest, those with lower levels of household income and educational attainment, those who are uninsured or insured by Medicaid, those experiencing psychological distress, and those who have a disability (49,184).

Smoking Prevalence by US Region



Source: (49).

W13

Furthermore, US adults who identify as belonging to the sexual and gender minority (SGM) population have higher rates of using tobacco products.

Similar to the trend in adults, tobacco use among US youth such as middle and high school students is also declining, with 6.6 percent of middle and 12.6 percent of high school students reporting current use of a tobacco product in 2023 (185). The number of high school students with current use of any tobacco product declined from 2.51 million in 2022 to 1.97 million in 2023, representing 540,000 fewer high school students using tobacco products (185). Specifically, the proportion of middle and high school students who have ever used a cigarette in 2023 was 4.3 and 8.5 percent, respectively, equating to 510,000 middle and 1.3 million high school students (185).

Flavored tobacco products, such as menthol cigarettes, pose a significant health risk, at least partly because they lead to increased nicotine dependence and reduced smoking cessation compared to nonmenthol cigarettes (186,187). Overall, 38.8 percent of Americans who smoke use menthol cigarettes and their use is more common in Black individuals (188). Evidence shows that young adults are more likely to try menthol cigarettes and are more likely to continue smoking into adulthood compared to young adults who try nonmenthol cigarettes (186). In addition, 40.4 percent of middle and high school students who smoke report using menthol cigarettes (185). This is greater than the percentage of adults who smoke menthol cigarettes.

There is strong evidence that smoking cessation has both immediate and long-term health benefits, especially when stopping at a younger age. Those who stop smoking reduce their risk of developing cancers of the larynx, oral cavity, and pharynx by half after 10 years of cessation (189,190). After 20 years, the risk of developing these cancers is lowered to the same level as someone who never smoked (189,190). Evidence from a large study demonstrated that, among individuals who stopped smoking before age 45, all-cause mortality was similar to that of a person who never smoked (191).

Evidence-based interventions at local, state, and federal levels, including tobacco price increases, public health interventions, marketing restrictions and bans on menthol cigarettes, subsidized smoking cessation counseling (such as through insurance), FDA-approved medications, and smoke-free laws, must be utilized to continue the downward trend of tobacco use (192).

Exposure to secondhand smoke, which occurs when people inhale smoke exhaled by people who smoke or from burning tobacco products, can cause cancer. Furthermore, exposure to secondhand smoke increases the risk of heart disease (8 percent), stroke (5 percent), and type 2 diabetes (1 percent) (193). Encouragingly, secondhand smoke exposure has declined in the United States from 27.7 percent between 2009 and 2010 to 20.7 percent between 2017 and 2018 (194), the most recent time for which such data were available. Despite this decline, secondhand smoke is estimated to cause 41,000 deaths each year among adults in the United States, with 7,300 deaths attributed to lung cancer (195). Enacting smoke-free laws that prohibit smoking in public places, such as in parks, restaurants, and public transit, can eliminate the risk of secondhand smoke and are essential to reduce the negative health effects on those who do not smoke.

It is estimated that **37 percent** of the global population is **exposed to secondhand cigarette smoke**, with higher exposure rates among women and children.

Source: (193).

W14

Electronic cigarettes, commonly known as e-cigarettes, were first introduced in the United States in 2006, and have gained popularity among those who have never used tobacco products. Since 2014, e-cigarettes have been the most used tobacco product among middle and high school students (196). In 2023, 10 percent of middle and high school students used e-cigarettes, with 25 percent of users reporting daily use of e-cigarettes (185). Of middle and high school students who used e-cigarettes daily, nearly nine out of 10 reported using flavored e-cigarette products (185). The primary drivers of use among adolescents were peer pressure and living with a person who uses tobacco (197). E-cigarettes are also popular among those who want to stop smoking; however, the benefits of e-cigarettes for smoking cessation are not as well established (198). More rigorous research evaluating the benefits of e-cigarettes in smoking cessation using randomized clinical trials is needed.

The landscape of e-cigarette devices has evolved over the years to include different types of products, such as prefilled pods (e.g., JUUL) or cartridge-based and disposable devices (e.g., Puff Bar), among others. E-cigarettes can deliver nicotine, a highly addictive substance that is harmful to the developing brain, much faster than traditional tobacco products (199).

Recent estimates show that e-cigarette usage was highest among individuals ages 18 to 24 years, with 18.6 percent reporting current use; among these, 71.5 percent of individuals ages 18 to 20 years had never smoked combustible cigarettes (200).

67 percent of adolescents (ages 12 to 18 years old) **who used e-cigarettes** within the previous year **tried to quit** with 63.7 percent quitting without assistance.

Source: (185).

W15

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 (201,202). Furthermore, people who use e-cigarettes are 3 to 4 times more likely to ever smoke a combustible cigarette than people who have never used e-cigarettes (202). 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.

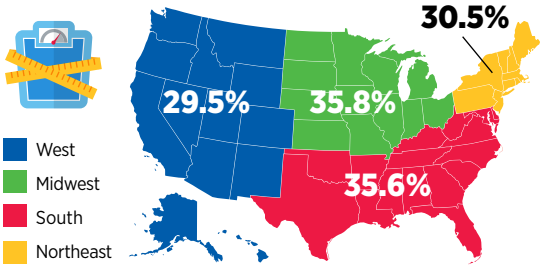
Another area in which more research is needed is the health consequences of smoking marijuana. For example, there is concern among public health experts that it could cause cancer because it involves the burning of an organic material, much like smoking tobacco (203). The need for this research is driven by the growing number of states that have legalized marijuana use for medical and/or recreational purposes. Currently in the United States, 74 percent of Americans live in a state where marijuana is legal for either recreational or medical use (204).

Use of cannabidiol (CBD), an active ingredient in marijuana, in e-cigarettes among US middle and high school students is particularly concerning, with 21.3 percent reporting use in the previous month (205). CBD use in e-cigarettes, often referred to as vaping, is higher among Hispanic and SGM populations (205). Although the cancer risk and other adverse health outcomes associated with vaping CBD are not well established, continued monitoring and research are needed.

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

More than 20 percent of new cancer cases and more than17 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 11**, p. 48) (48,206,207). Following a healthier lifestyle may reduce the risk of developing certain cancers as well as many other adverse health outcomes.

Prevalence of Obesity by Region of the United States



Source: (217).

W16

GLOBALLY, BETWEEN 2010 AND 2019, THERE WAS A 35% INCREASE IN DEATHS FROM CANCERS ATTRIBUTABLE TO BEING OVERWEIGHT.

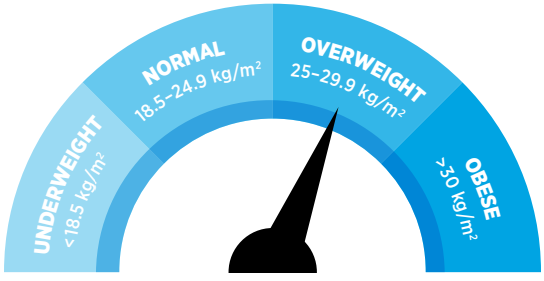
Source: (218).

W17

Excess body weight is responsible for 7.6 percent of all cancers (48). Among US adults, the rate of obesity during 2017 to 2020 was 41.9 percent (215). This is a 37 percent increase from the year 2000, when the rate was 30.5 percent (215). During this same time, severe obesity among US adults nearly doubled, with an increase from 4.7 percent to 9.2 percent (215). Globally, rates of obesity have doubled between 1990 and 2022, with 16 percent of adults over the age of 18 who were obese in 2022 (216). As with smoking, adults who are obese have an increased risk of many chronic diseases, including diabetes, cardiovascular disease, stroke, and cancer (84).

Weight loss interventions have proven effective in reducing or eliminating the risk of cancers associated with obesity (219,220).

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 distinguish between underweight, healthy weight, overweight, and obesity**.

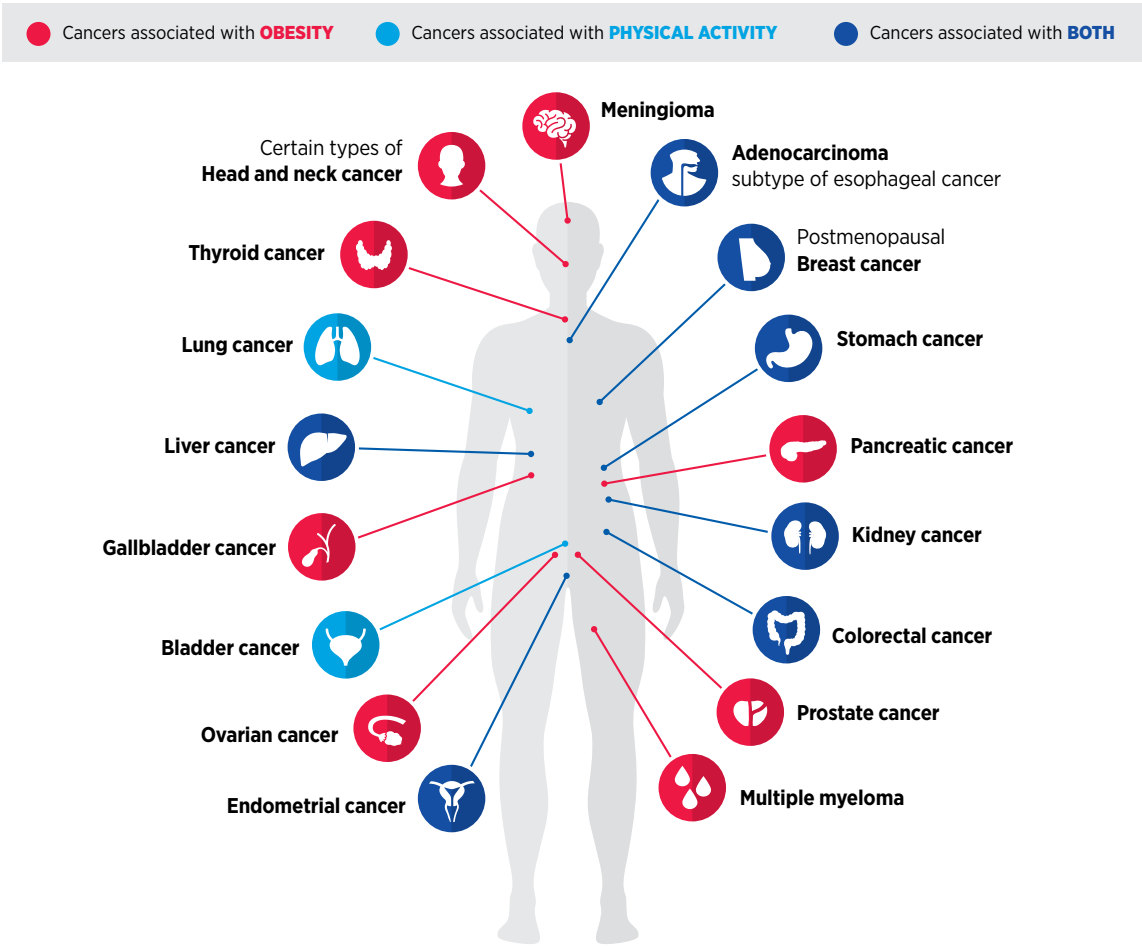


BMI has historically been used to measure obesity because it was simple to calculate. However, it **may over- or underestimate body fat for certain individuals**. Researchers have begun using other metrics such as waist to hip ratio, which is more accurate for more people.

W18

FIGURE 11

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 colorectal, 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.

Source: (1, 208-214).

Bariatric surgery is a collection of procedures that are done to help people who are obese lose weight when effectively paired with eating a healthy diet and regular exercise. Bariatric surgery has been shown to lower the risk of developing and/or dying from certain obesity-associated cancers (221,222).

Another type of weight loss strategy that has been on the rise is the use of weight loss drugs such as semaglutide (brand names Ozempic and Wegovy). These drugs, called GLP-1 receptor agonists, work by mimicking the hormone GLP-1, which controls the body's insulin levels and leads to appetite suppression and feeling fuller for longer periods of time after eating. These drugs, in combination with eating a healthy diet and exercise, have led to dramatic weight loss for many individuals.

Although the effect of these drugs on weight loss are encouraging, more research is required to understand whether these medications can reduce the rates of obesity-associated cancers. In this regard, studies evaluating the long-

term effects of GLP-1RA (a drug very similar to semaglutide) among diabetic patients demonstrate their potential to reduce the risk of cancer (223). After 15 years of follow-up, researchers found that the risk of colorectal cancer in patients who were given the therapeutic decreased by half compared to patients who received other types of diabetic medication (e.g., insulin) (223). While this research is promising, it is important to note that no long-term studies of these treatments have been done with non-diabetic patients. It will be important to continue monitoring the long-term effects of these weight loss medications in non-diabetic patients and their ability to reduce obesity-related cancers.

Poor diet, consisting of red meat and processed foods and lacking fresh fruits or vegetables, is responsible for the development of more than 4.2 percent of all cancers, with several studies demonstrating a link between consumption of highly processed foods and increased cancer incidence (48,224-226).

The widespread availability and low cost of fast food—food that can be prepared quickly and easily and that is sold in restaurants and snack bars as a quick meal or to be taken out—led to 37 percent of US adults (ages 40 to 59) and 45 percent of US young adults (ages 20 to 39) consuming fast food on any given day during 2013–2016 (227). Unfortunately, fast foods are often of poor nutritional value, calorie dense, high in salt content, and low in fiber (228-230).

Intake of red meat specifically should be limited to no more than three servings a week (12 to 18 ounces a week) and should not include processed meats (e.g., hot dogs, bacon, and salami), because these foods can increase the risk of colorectal, rectal, and potentially other cancers including prostate and pancreatic cancer (228-233). Sugar-sweetened beverages, 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 increasing the risk of several cancers including liver and colon cancers, as well as other chronic diseases including diabetes and kidney disease (234-240). High fructose corn syrup, a common ingredient used as a sweetener in many processed foods and beverages, has also been found to promote intestinal tumor growth in experimental models, although more research, including epidemiological data in humans, is warranted (241).

One strategy to lower consumption of foods high in sugar is to implement taxes on sugar-sweetened beverages, such as those introduced in several cities in the United States. In cities with such taxes, significant reductions were made in the consumption of sugar-sweetened beverages compared to cities that did not implement these types of taxes (242-244). As of 2022, eight US jurisdictions and more than 50 countries have implemented some type of tax on sugar-sweetened beverages (243). Pilot initiatives such as these are a step in the right direction and continuous evaluation will further determine their long-term health benefits and impact on diet, obesity, and cancer burden.

Consuming **one or more sugar-sweetened beverages a day** was found to **increase the risk of liver cancer** by 1.8 times compared to not drinking any sugar-sweetened beverage.

Source: (234).

W19

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 (245,246) (see **Sidebar 10**, p. 50). One study of nearly 80,000 men from diverse backgrounds found that adherence to a healthy diet lowered risk for certain types of colorectal cancers (247). Increasing access to healthy foods such as by eliminating food deserts, which are geographical areas with a low density of grocery stores; promoting the benefits of healthy foods in decreasing the risk of cancer and other chronic diseases through public education campaigns and initiatives; and reducing government subsidies for crops like corn and soybeans, which are used to make inexpensive sugars, including corn syrup, that are used in highly processed foods in favor of subsidies for whole foods like fruits and vegetables are imperative to improve Americans' diets and reduce the risk and incidence 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 11**, p. 51) (248,249). One study found that among 500,000 people who participated in a balanced combination of moderate and vigorous aerobic and muscle strengthening exercises, there was a 50 percent lower rate of all-cause and cancer-specific mortality (248).

When compared to those who did not participate in physical activity, **women reduced their risk of breast cancer by 18 percent** with occasional exercise, **31 percent** with moderate exercise, and **40 percent** with high levels of exercise.

Source: (250).

W20

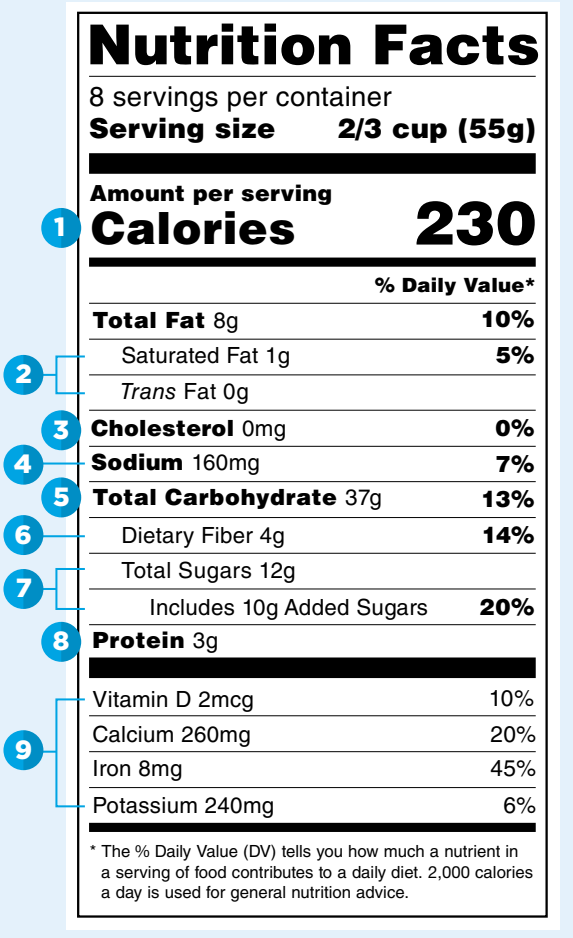
SIDEBAR 10

Making Healthy Food Choices: Nutrition Labels

Nutrition labels found on food packaging break down the number of calories, and the amount of carbohydrates, fat, fiber, protein, and vitamins per serving of food. Because these labels are required to appear on most packaged foods, it is easy to compare different products quickly. In general, eating foods with high amounts of vitamins, minerals, and fiber and little to no added preservatives are the healthiest option. It is better to avoid products that are high in sodium, added sugars, and saturated and trans fats. For more information about the newest guidance on reading food labels, visit **www.fda.gov/NewNutritionFactsLabel**.

Nutrition facts information

1. The number of **calories** in a food directly **reflects the energy** it contains.
2. **Fat** is a central component of nutrition; however, high levels of saturated and trans fats, commonly found in processed foods, **can raise cholesterol levels, increase risk of chronic conditions, and lead to obesity, which raises the risk of cancer**.
3. **Cholesterol** is a type of fat that the body needs to work properly. While cholesterol in food does not increase blood (i.e., serum) cholesterol, in general high levels of serum cholesterol **can lead to heart disease, stroke, and other problems**.
4. **Sodium** controls blood pressure and blood volume. However, foods high in sodium, such as processed meats (e.g., hot dogs, bacon, and salami), **can increase risk for colorectal and possibly other cancers**.
5. **Carbohydrates** are an essential part of food because the body uses them as **a source of energy.**
   - **Simple carbohydrates**, such as those found in white bread, pastries, sodas, and other highly processed or refined foods, **contribute to weight gain and promote diabetes, which can increase the risk of cancer**.
   - **Complex carbohydrates**, such as those found in whole grains, vegetables, fruits, and beans, **promote health** and are also sources of vitamins, minerals, fiber, and other nutrients.
6. A diet rich in **fiber** is low in calories and **promotes a healthy weight**. Common sources of fiber include whole grains, fruits, and vegetables.
7. **Sugars** occur naturally in fruits, honey, and milk and can be present in all types of foods. However, high levels of added sugar, like those in sugar-sweetened beverages, **contribute to prolonged elevated blood sugar and insulin resistance, increasing the chance of developing diabetes and becoming overweight, which can raise the risk of cancer**.
8. **Proteins** are essential to **maintain and replace tissues** and **can be used as a source of energy** if the body is not getting enough calories from carbohydrates or stored fat.
   - **Proteins contain essential and nonessential amino acids.** Essential amino acids are vital in a diet because the body cannot make them.
   - **Incorporating protein** from sources such as quinoa, soy, and buckwheat, **which contain both essential and nonessential amino acids, promotes health**.



9. **Vitamins** are derived from plants and animals and perform many functions in the body, including **keeping nerves healthy, helping the body get energy from food, and managing blood clots**.
   - **Minerals** are derived from rocks, soil, or water but can be present in foods. Minerals like fluoride or calcium **strengthen bones and prevent cavities**.
   - Eating a diet rich in **vitamins and minerals** from fruits and vegetables **drastically reduces cancer risk**.

SIDEBAR 11

Physical Activity Guidelines

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

Pre-school aged children
(3–5 YEARS)

Adolescents
(UNDER 18 YEARS)

Adults
(18–64 YEARS)

Older adults
(65+ YEARS)

	Adolescents (UNDER 18 YEARS)	Adults (18–64 YEARS)	Older adults (65+ YEARS)
Aerobic Activity			
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.	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
- Pickle ball

VIGOROUS INTENSITY

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

- Running
- Swimming fast
- 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: (1).

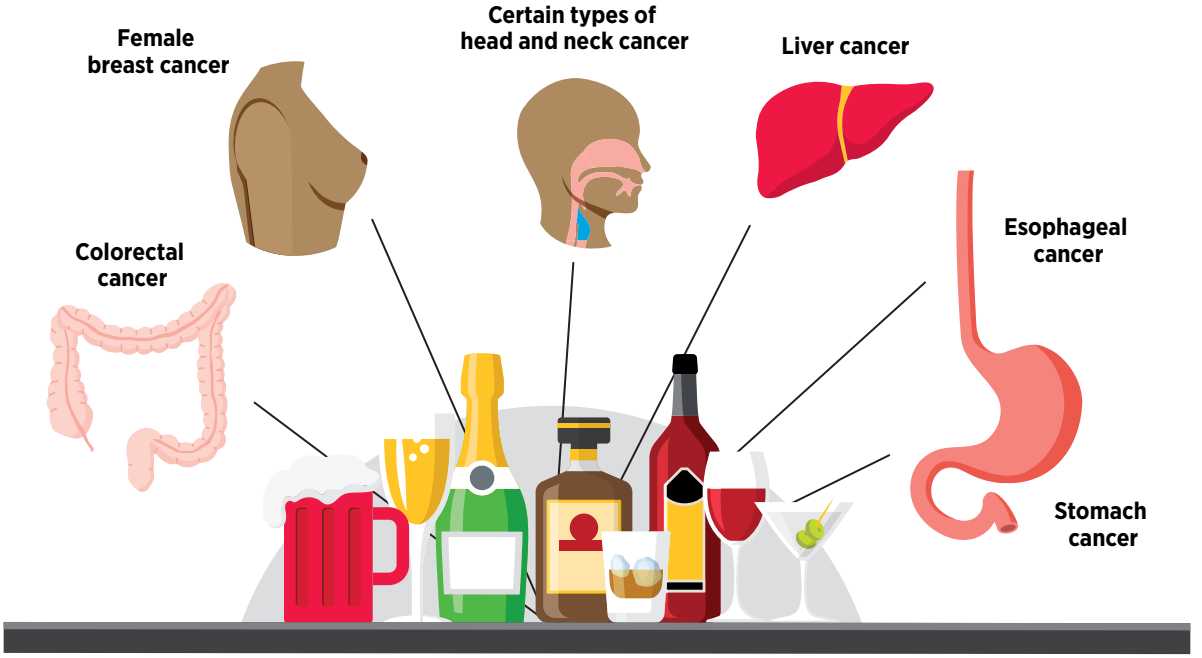
There are many barriers that may prevent individuals from being physically active, including cost and access to fitness facilities, low neighborhood walkability, lack of green spaces, inadequate tree canopy cover, and family obligations (251-254). These barriers are exacerbated in racial and ethnic minority individuals and medically underserved populations. Based on recent data, physical inactivity is higher among Hispanic (31.7 percent) and non-Hispanic (NH) Black (30.3 percent) populations, compared to those who are NH White (23.4 percent) (255). There are also geographic disparities, with only 16 percent of people in suburban and rural areas meeting the recommended physical activity guidelines, compared to 27.8 percent of those living in urban areas (256).

A sedentary lifestyle can increase the risk of certain cancers. As one example, researchers found that a person's risk of pancreatic cancer was increased in a proportionate manner for every hour spent watching television, which was used as a measure of sedentary behavior (257). The study further showed that the more an individual watched television, the higher their BMI was, which partially explains why sedentary behavior like watching television increases pancreatic cancer risk (257).

Developing widespread public health campaigns to increase physical activity in the US population is vital if we are to change the current trends of sedentary lifestyles. As one example, The Active People, Healthy Nation initiative in the United States aims to help 27 million people become

FIGURE 12

Alcohol and Cancer Risk



Consumption of alcohol increases an individual's risk of developing six types of cancer—certain types of head and neck cancer, esophageal squamous cell carcinoma, and breast, colorectal, liver, and stomach cancers.

more physically active by 2027 by designing activity-friendly communities, encouraging physical activity at school, and consulting community leaders to implement relevant programs to encourage physical activity.

Reduce Alcohol Consumption

Excessive levels of alcohol consumption increase the risk for six different types of cancer (see **Figure 12**, p. 52) and is linked to more than 200 diseases. In the United States, 5.4 percent of cancers were attributed to alcohol consumption, in 2019, the most recent year for which data are available (48). Of concern, a recent survey found that 51 percent of Americans did not know that the consumption of alcohol increases the risk of certain types of cancer, such as colorectal cancer (258).

Research indicates that those who reduce alcohol consumption or stop drinking altogether can decrease their risk of developing alcohol-related cancers by 8 percent and can reduce their risk of all cancer by 4 percent compared to those who sustain or increase their consumption of alcohol (259). Public messaging campaigns (such as cancer-specific warning labels displayed on alcoholic beverages) along with effective clinical strategies that reduce or eliminate alcohol consumption must be considered to reduce the burden of alcohol-related cancers (see **Sidebar 12**, p. 53).

Brief counseling interventions delivered in primary care settings can reduce excessive alcohol consumption (260). In addition, more complex behavioral interventions and evidence-based medical interventions are effective tools in treating alcohol use disorder, though these strategies are often under-utilized despite their effectiveness in reducing alcohol consumption (261).

Protect Skin From UV Exposure

Ultraviolet (UV) radiation is a type of light emitted primarily from the sun but also from artificial sources, such as tanning beds. Exposure to all sources of UV radiation can lead to the development of skin cancers, including basal cell carcinoma, squamous cell carcinoma, and melanoma, which is the most aggressive form of skin cancer. In 2024, there will be an estimated 100,640 new diagnoses of melanoma of the skin and 8,290 deaths (see **Table 1**, p. 17).

SIDEBAR 12

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,* do not recommend that individuals who do not drink alcohol start drinking for any reason. There are also some people who should not drink at all, such as those who are pregnant or might be pregnant; 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 or if they are unable to control the amount they drink.

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

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:

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

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

HEAVY DRINKING

EXCESSIVE ALCOHOL CONSUMPTION

≥ 4 drinks within 2 hours for women

≥ 5 drinks within 2 hours for men

BINGE DRINKING

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

Source: (1,262).

Ultraviolet radiation accounts for 95 percent of skin melanomas and 4.6 percent of all cancers (48,206). This is because UV radiation can damage cellular DNA, with continued exposure leading to cancer. Anyone can develop skin cancer, but some people are at a higher risk, especially those who are light skinned and get easily sunburned.

It has been reported that there is a lack of understanding in the US population regarding how skin cancer develops and when to use sun protection (263). According to data from CDC, 29 percent of US adults and 64 percent of adolescents experienced sunburn at least once in the past year in 2021 (264,265). This is concerning, as severe sunburn increases the risk of developing all three types of skin cancer (up to two and a half times for melanoma), compared to no history of severe sunburn (266). One study reported that women who experienced at least five episodes of severe sunburns between the ages of 15 and 20 years were 80 percent more likely to develop melanoma later in life, compared to those who did not experience sunburns (267).

One 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 practice sun-safe habits anytime they are outside to limit exposure to harmful UV radiation (see **Sidebar 13**, p. 54).

Indoor tanning exposes individuals to the same harmful UV radiation as from the sun but in an artificial setting. Fortunately, rates of indoor tanning have been declining over the past decade, particularly among US youth (268). Currently, 44 states and the District of Columbia either ban or regulate the use of indoor tanning devices by minors (269). All states should enact legislation banning indoor tanning for minors, to continue the downward trend of tanning bed usage, especially among youth.

SIDEBAR 13

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; Look for sunscreen that is **SPF 30 or higher**, offers "broad-spectrum" protection, and is water resistant. Sunscreen should be applied 15 minutes prior to going outside.

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

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 3**, p. 55). Infection with these agents can change the way a cell behaves, weaken the immune system, and cause chronic inflammation, all of which can lead to cancer. In the United States, about 3.4 percent of all cancer cases are attributable to infection with pathogens (48). Globally, an estimated 13 percent (2.2 million) of all cancer cases in 2018 were attributable to pathogenic infections, with more than 90 percent of these cases attributable to four pathogens: human papillomavirus (HPV), hepatitis B (HBV), hepatitis C (HCV), and *Helicobacter pylori* (212).

Individuals can significantly lower their risks by protecting themselves from infection through preventive measures such as vaccination or by seeking treatment, if available, to eliminate an infection (see **Sidebar 14**, p. 56).

HPV is a group of more than 200 related viruses that are responsible for almost all cervical cancers, 90 percent of anal cancers, and 70 percent of oropharyngeal cancers, as well as most penile, vaginal, and vulvar cancers. While most HPV infections do not cause cancer, infection with high-risk strains of HPV for long periods of time (i.e. persistent infection) can lead to cancer. There are at least 12 high-risk HPV types and include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 with HPV 16 and 18 being responsible for most HPV-related cancers (270). These high-risk HPVs cause 1.2 percent and 2.5 percent of all cancers in men and women, respectively, in the United States (48). Globally, HPV-related cancers make up about 5 percent of all cancers (270).

The HPV vaccine is approved for males and females ages 9 to 45, with recommendations for the first doses beginning at age 11 to 12 (see **Sidebar 16**, p. 62). The HPV vaccine currently used in the United States, Gardasil 9, can protect against nine of the 12 high-risk HPV strains (see **Human Papillomavirus and AYA Populations**, p. 61).

Chronic infection from HBV and HCV can cause liver cancer and can be a risk factor for other malignancies, such as non-Hodgkin lymphoma. Globally, the most common risk factor for liver cancer is chronic infection with HBV and HCV. In the United States, after new reported cases of HBV remained stable from 2013 through 2019, there was an abrupt decrease of 32 percent in reported cases in 2020, with a further decrease of 14 percent between 2020 and 2021 and another decrease of 6 percent in 2022 (271). These decreases are potentially attributable to the COVID-19 pandemic, which may have led to reduced testing but not necessarily reduced infections (272).

For the first time since 2015, cases of acute HCV infection decreased 6 percent between 2021 and 2022 (271). Despite this modest decrease, rates of acute HCV infection are still two-fold higher than the rates in 2015 and are highest among persons ages 30 to 39 (271). 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.

Helicobacter pylori (H. pylori) is a type of bacteria that has been shown to cause gastric cancer if left untreated. This is due to inflammation of the gastric (i.e., stomach) tissue caused by *H. pylori* infection that, when present for an extended

TABLE 3

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	810,000
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	360,000
Hepatitis C virus (HCV)	Hepatocellular carcinoma and other cancers	156,000
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	690,000
Human T-cell lymphotrophic virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma	3,600
Merkel cell polyomavirus (MCV)	Skin cancer	N/A

Source: (1).

period, increases the likelihood of two types of cancer, gastric adenocarcinoma and gastric mucosa–associated lymphoid tissue (MALT) lymphoma, a rare type of non-Hodgkin lymphoma. *H. pylori* infection is higher among AI/AN communities. Among Navajo adults in Arizona, the *H. pylori* prevalence is 62 percent, while 74 percent of the Alaska Native population are reportedly infected with *H. pylori*, compared to 36 percent in the overall US population.

Large bodies of evidence have demonstrated a link between chronic *H. pylori* infection and the development of cancer. In geographic regions where there are high rates of *H. pylori* infection, such as in Asian countries, residents have a higher risk of gastric cancer (273). Other 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 (274). 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 (275-277).

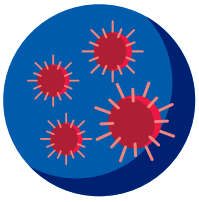
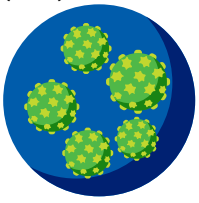
Fortunately, overall, new cases of *H. pylori*–associated gastric cancer have declined at a rate of 1.5 percent each year for the past decade; however, rates of *H. pylori*–associated gastric cancer are not equal among all population groups (278,279). Among those diagnosed with *H. pylori* infection, racial and ethnic minority populations and those who smoke are at a greater risk of gastric cancer (280).

Limit Exposure to Environmental Risk Factors

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. However, some individuals experience higher levels of exposure to certain pollutants due to their living conditions and/or daily activities. Environmental carcinogens, which are substances that can lead to cancer and are present in

SIDEBAR 14

Ways to Reduce Cancer Risk From Pathogens

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

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: (1).

the environment, include 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 (NTP) are both responsible for evaluating substances and exposures and classifying them as carcinogens at the global and national level, respectively.

Radon is responsible for 21,000 lung cancer deaths every year, with 2,900 deaths occurring in people who have never smoked.

Source: (285).

W21

Of increasing concern among public health experts is climate change, which refers to a change in temperature and weather patterns across the globe because of human activity. There is strong scientific evidence that climate change is occurring, and that it has the potential to worsen exposure to carcinogens. For instance, wildfires in the western United States and Canada, which have increased in intensity in recent years due to climate change (281), have led to increased exposure to certain metal toxins, such as carcinogenic forms of chromium known to increase cancer risk (282).

Radon is a naturally occurring radioactive gas that is produced from the breakdown of uranium in soil, rock, and water. Radon gas can seep into homes through cracks in the floor or walls and through gaps around pipes, wires, or pumps. The levels of naturally occurring radon vary widely based on geographic location and are highest in areas rich in radioactive ore. Additionally, byproducts from previous mining of uranium—for example in the Southwest— have led to increased levels of radon in nearby areas (177).

Radon is the number one cause of lung cancer among non-smokers and is the second leading cause of lung cancer overall, contributing to approximately 12 percent of lung cancers in the United States annually (283-285).

Radon testing using approved test kits, especially in crawl spaces and basements where radon is most concentrated, should be used to mitigate exposure. EPA maintains a database of resources available to obtain radon testing kits, sometimes at little to no cost.

Living near industrial areas can increase 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 (175,176,286-288).

Air pollution is contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere with major pollutants including particulate matter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. In 2013, IARC concluded that particle pollution may cause lung cancer and subsequently classified it as a potential cause of cancer in humans (289,290). Air pollution may also be attributable to polycyclic aromatic hydrocarbons (PAHs), which are chemicals that have been associated with several cancers, including cancers of the lung and breast (291,292).

In 2024, 131.2 million people lived in places with unhealthy levels of particulate pollution and 63.7 million people living in the United States were exposed to daily, unhealthy spikes in particle pollution (30). This equates to 11.7 percent more people exposed to daily, unhealthy spikes compared to 2023 (30). Low-income populations and racial and ethnic minority groups are among those who often experience higher exposure to pollutants (30,173,174). 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 lung cancer (175,176).

Increasingly, the use of flame-retardant compounds in car interiors, building materials, and other consumable products are being recognized as carcinogenic. Several studies have demonstrated that these compounds are linked to increasing cancer risk, with one study showing consistent exposure to a common flame retardant significantly increased the risk of cancer mortality by 300 percent (293,294).

The endocrine system is made up of the glands and organs that make hormones and release them directly into the blood so they can travel to, and regulate the functions of, body tissues and organs. Endocrine-disrupting chemicals can be natural or human-made, and may mimic, block, or interfere with the body's hormones. Endocrine-disrupting chemicals, such as per- and poly-fluoroalkyl substances (PFAS) or chlordane, hexachlorocyclohexane, and polychlorinated biphenyls, have been shown to increase the risk of certain cancers, such as thyroid and breast cancers (287,288). An emerging concern is the use of personal care products, such as hair straightening products, which contain hazardous chemicals with endocrine-disrupting properties and are associated with increased risk of uterine and breast cancers (295-297).

Drinking water can also contain contaminants including PFAS, asbestos, arsenic, radon, agricultural chemicals, and hazardous waste (298). American Indian or Alaska Native (AI/AN) individuals are 19 times more likely than White individuals to live in a household without indoor plumbing, requiring them to source water from communal wells (299,300). These water sources are more prone to being contaminated with bacteria, arsenic, and uranium (299,300), all of which increase the risk of several types of cancer, including gastric, liver, lung, bladder, and kidney cancers (298,299,301). Evidence also demonstrates that pollution with PFAS is higher in communities in proximity to polluting

industries such as airports, industrial sites, wastewater treatment plants, and military fire training areas (302).

Coordinated efforts such as those being initiated by Cohorts for Environmental Exposures and Cancer Risks, build collaborative infrastructure, and facilitate integrated scientific research for enhancing the understanding of environmental exposures influencing cancer etiology, and the genetic, behavioral, and structural factors that modify risk across diverse populations.

Higher than normal levels of exposure to carcinogens have led IARC to classify certain occupations, such as firefighting and industrial painting, and work environments, such as iron and steel foundries or working around welding fumes, as class 1 carcinogens, meaning they are cancer-causing to humans. For instance, firefighters are at a greater risk of developing several types of cancer because of the constant exposure to smoke and other hazardous materials (303,304). To reduce the risk of occupational exposure to carcinogens, workers should consistently wear personal protective equipment (PPE) that reduces or eliminates their exposure and decontaminate PPE after working in environments with carcinogens and other hazardous materials.

Other risk factors associated with a person's occupation, including lack of sleep and night-shift work, have also been shown to increase their risk of developing certain types of cancers and other chronic diseases including diabetes and obesity (305). CDC reports that about 11 million adults in the United States frequently work night shifts, with certain groups, such as men, and Black and non-Hispanic individuals, more likely to do this type of work. In one recent study, researchers found that women age 50 or older who worked both day and night shifts were twice as likely to develop breast cancer as those who only worked day shifts (306).

Although the underlying mechanisms are not clear, researchers believe that disruption of the body's circadian rhythm (i.e., the internal clock) can alter biological processes that normally prevent cancer development (307). Emerging research indicates that avoiding lighting that disrupts circadian rhythms, for example, lighting that is low in blue light, may help reduce cancer risk (308-310). Long-term research is needed to understand how avoiding exposure to certain light sources, particularly at night, may help regulate the circadian rhythms and thus may reduce cancer risk.

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

Be Cognizant of Hormonal Factors

Pregnancy and Breastfeeding

Studies have shown that a woman's risk of developing breast cancer is associated with reproductive factors such as pregnancy and breastfeeding that regulate their exposure to estrogen and progesterone, two hormones produced by their ovaries. Evidence has shown that women who have given birth are at a reduced risk of developing estrogen receptor–positive (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 (311-313).

During the period immediately following pregnancy, women are at an elevated risk of developing pregnancy-associated breast cancers, which refer to breast cancers diagnosed during gestation, lactation, and within five years postpartum (314). Evidence has demonstrated that both estrogen receptor–negative (ER–) tumors and triple-negative breast cancer are the most common subtypes of pregnancy-associated cancers (311,313,315). In the United States, there are about 3,500 cases of pregnancy-associated breast cancer each year (314). 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 (316).

Breastfeeding, specifically lactation, has been linked with a reduced risk of breast cancer (317-319), with increased duration of breastfeeding associated with further decrease in risk (212,313,318,320-322). A recent analysis evaluating the association of pregnancy and breastfeeding with the development of breast cancer found that breastfeeding was consistently associated with decreased risk of all subtypes of breast cancer (323). However, this risk differed across race and ethnicities.

Fully understanding the relationship of pregnancy and breastfeeding with the risk of breast cancer in women will be important to implement interventional strategies that can reduce this risk.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) refers to treatments that aim to relieve the common symptoms of menopause and the long-term biological changes, such as bone loss, that take place after menopause. These changes occur due to the decline in 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 is because when

estrogen is given alone, but not in combination with progestin, it is associated with an increased risk of endometrial cancer, a type of cancer that forms in the tissue lining of the uterus.

Data show that women who use the estrogen and progestin combination have an increased risk of developing breast cancer (324,325). 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 (326-328). 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 (327). Individuals who seek HRT should discuss with their health care providers the advantages and possible risks, before deciding what is right for them.

One area of ongoing investigation in exogenous hormone use is the differential cancer risks among individuals undergoing gender-affirming hormonal therapy (GAHT) (329). While current data are limited, there is emerging evidence indicating an increased risk of breast cancer, but a lower risk of prostate cancer, among trans women who received GAHT compared to age-matched cisgender men. Trans men who received GAHT had a lower risk of breast cancer compared to age-matched cisgender women (330,331). New evidence indicates that this lower risk of breast cancer in trans men may be due to protective effects of receiving androgen therapy during their transition (332). Long-term population-based studies are needed to comprehensively assess the risk of cancers in these understudied and medically underserved populations.

★ SPOTLIGHT

Increasing Cancer Risk Among Children and AYAs

Inherited genetic mutations play an important role in cancer development in children and AYA. Modifiable risk factors play a far less critical role in the development of childhood cancers compared to cancers in adults. Regardless, there is some evidence that exposure to certain modifiable factors can increase the risk of cancer among children, as discussed below.

AYA individuals can be exposed to the same types of modifiable cancer risk factors as adults. When combined with genetic predispositions, e.g., Lynch syndrome (see **Genetic Alterations**, p. 31), such exposures can further increase the risk of cancer development. There has been a rise in certain types of early-onset cancers caused by a combination of factors including genetic predisposition, diet, and obesity. Infection with certain pathogens can also increase the risk of cancer in this group (see **Sidebar 15**, p. 60). This section discusses the unique risk factors faced by children and AYA individuals.

Tobacco Use in Children and AYAs

Exposure to smoking and its byproducts, either in the womb or through secondhand smoke exposure, can increase cancer risk for children and AYAs (338-342).

Smoking during pregnancy can lead to many adverse health effects, including complications such as birth defects, premature birth/low birth weight, damage to the organs of the developing fetus, and increased risk of cancer after the child is born (339-343). As one example, it has been observed that mothers who are pregnant and smoke increase the risk of brain and central nervous system tumors after the birth of the child (344). Another study found that maternal smoking during pregnancy doubled the risk of gliomas and tripled the risk of retinoblastomas in children 5 years or younger (345).

Secondhand smoke, which can cause spontaneous miscarriage in pregnant women, can increase the risk of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (341,347-349). Secondhand smoke exposure among children has also been found to increase the development of lung cancer in adulthood (350).

Smoking during adolescence is a strong predictor of continued tobacco use as an adult, and smoking in AYA populations can increase the risk of cancer, particularly lung cancer, during adulthood (see **Eliminate Tobacco Use**, p. 44). US states that have a higher prevalence of smoking among AYA groups have higher rates of cancer, independent of educational attainment, employment, or economic status (351).

Body Weight, Diet, and Physical Activity in Children and AYAs

Although being overweight or obese does not necessarily lead to cancer in children and adolescent groups, data show that being overweight or obese during

CHILDREN WHO ARE EXPOSED TO PARENTAL SMOKING
AND DEVELOP
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
HAVE LOWER 5-YEAR SURVIVAL.

Source: (346).

W22

SIDEBAR 15

What Is Causing the Rise in Early-onset Cancers?

Each year in the United States, an estimated 18,000 people under the age of 50 are diagnosed with an early-onset cancer, a trend that has been on the rise since 1995. While researchers are not sure of the exact reason for this rise, several factors are under investigation:

Unhealthy diet and the microbiome

Obesity

Chemicals in the environment

Use of antibiotics

Alcohol

Sedentary behaviors

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

Source: (17, 333-337).

this stage of life increases the likelihood of developing cancer as an adult (352). For instance, men with high BMI at the age of 18 were more likely to develop cancers as older adults (on average, 30 years later) compared to those with a normal BMI (353). Another study found that weight gain after the age of 18 increased breast cancer incidence in postmenopausal but not in premenopausal women (354). Therefore, the rise in obesity among children and teens (2 to 19 years of age) in the past five decades, from 5 percent in the 1970s to approximately 19.7 percent during the period between 2017 and 2020 is concerning (355). It is imperative that all stakeholders work together to address the rise in obesity among all age groups, with early interventions among the youngest and most vulnerable being essential to reducing obesity as adults.

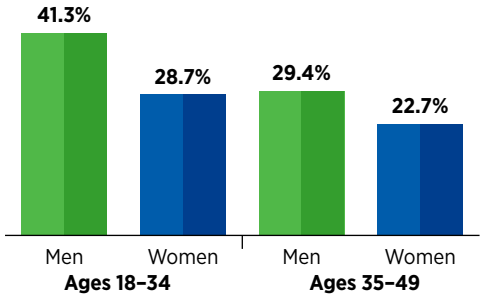
In AYA populations, there is a worrying increase in early-onset cancers, which research indicates is due to a combination of genetic risk factors coupled with the obesity epidemic, poor diet, and a lack of physical activity (see **Sidebar 15**, p. 60). Of particular concern is the recent rise in early-onset colorectal cancer (EOCRC). In the United States, rates of EOCRC are expected to double by 2030 among those 29 to 35 years old, while rates in older adults are expected to decrease (18,356,357). Although mechanisms are not entirely known, it is becoming increasingly clear that genetics, coupled with modifiable risk factors such as obesity and alcohol, is attributable to the rise in EOCRC (358-360).

Eating a healthy diet can help reduce the risk of many chronic conditions, including cancer (see **Maintain a Healthy Weight, Eat a Healthy Diet, and Stay Active**, p. 47). Unfortunately, compared to other age groups, the diet quality of adolescents is poor, with elevated consumption of foods that are high in fat and refined carbohydrates and low in fiber, and inadequate consumption of fresh fruits and vegetables (361,362). The poor uptake of healthy foods among this population can be due to numerous factors, including food insecurity, family dietary habits, convenience, and lack of affordable access to healthy foods (363). The poor dietary patterns can carry on into adulthood and increase the risk of many obesity-associated cancers (361) (see **Maintain a Healthy Weight, Eat a Healthy Diet, and Stay Active**, p. 47) (364,365). Reducing or eliminating consumption of highly processed foods, fast foods, and foods and beverages high in sugar is essential to curbing the obesity epidemic and reducing the burden of associated cancers.

Emerging evidence has demonstrated that antibiotics, which are commonly prescribed to eliminate bacterial infections, may increase the risk of early-onset colorectal cancer (366-368). Higher rates of antibiotic consumption among those younger than 50 years of age were associated with an increase of 1.5 times in colon cancer incidence compared to an increase of only 1.1 times in those older than 50 (367). While the mechanisms of this increase are not well understood, researchers believe that antibiotics disrupt the normal gut bacteria, called the microbiome, upsetting the careful balance that promotes a healthy digestive system.

Key to maintaining a healthy weight and reducing the risk of cancer in all age groups is meeting the recommended CDC guidelines for physical activity (see **Sidebar 11**, p. 51). Unfortunately, 20 percent of US children ages 6 to 17 do not meet the guideline of a minimum of 60 minutes of exercise per day (369). This is concerning because childhood physical

PERCENTAGE OF YOUNG ADULTS WHO MET THE RECOMMENDED CDC EXERCISE GUIDELINES IN 2020



Source: (375).

W23

activity level predicts future physical activity levels as an adult (370-372). Further evidence has linked low physical activity levels at a young age with the risk for developing cancer as an adult (373,374). Lower levels of exercise are also observed among young adults and adults, with only one third of young adults meeting the recommended physical activity guidelines. Unfortunately, the amount of exercise only trends downward among those ages 35 to 49.

Regular exercise can improve overall health and reduce negative health outcomes for all age groups; however, adopting healthy exercise patterns early on in life can reduce the likelihood of chronic diseases, including cancer, in adulthood.

Alcohol Exposure in Children and AYAs

For women who are pregnant, alcohol consumption can affect the developing fetus and increase the risk of childhood cancer after birth. Research has shown an association between the degree of alcohol consumed during pregnancy and the likelihood of the child developing leukemia after birth up to the age of 14 (376,377). A large meta-analysis found that moderate drinking during pregnancy increased the risk of AML in offspring by 1.6 times, while high alcohol consumption increased AML risk by 2.4 times (377).

Alcohol intake at an early age can increase the risk of cancer later in life (378,379). One study found that those who have high consumption of alcohol in early adulthood increased the risk of early-onset colorectal cancer 1.5 times compared to those who did not consume alcohol even after adjusting for other factors like smoking (336).

The rise in early-onset cancers has also been attributed to the consumption of alcohol earlier in life; however, the research is still ongoing to confirm these findings (60,379-381). Continued research into the effects of alcohol exposure on cancer risk in children and AYAs is necessary to reverse the upward trend of early-onset cancers.

Human Papillomavirus and AYA Populations

Thanks to the development of the HPV vaccine nearly two decades ago, those who receive the vaccine as children nearly eliminate their risk of developing HPV-associated cancers. The HPV vaccine is approved for males and females ages 9 to 45, with recommendations for the first doses beginning at age 11 to 12 (see **Sidebar 16**, p. 62).

Despite clear evidence showing that the HPV vaccine reduces cervical cancer incidence, the uptake of the vaccine has been suboptimal in the United States (382). This is partly because there is no national mandate in the United States requiring HPV vaccination to attend school. However, some states have implemented their own vaccine requirements. As of 2024, four US states (Hawaii, Rhode Island, Virginia, and the District of Columbia) require the vaccine for entry into secondary schools. Rural areas have very low rates of HPV vaccination among teens, necessitating culturally tailored interventions to increase vaccination in these populations (383).

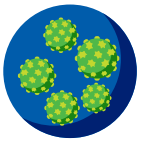
In 2022, only 62.6 percent of eligible children and adolescents (ages 13-17 years) had received the recommended two doses (384). While these numbers have improved compared to past years, rates of HPV vaccination in the US have been lower than in other countries such as the United Kingdom (UK) and Australia. In 2022, in the US, only 38.6 percent of children ages 9 to 17 had received one or more doses of the HPV vaccine, compared to 76.5 percent of children in the UK and 84.2 percent of children in Australia (385-387). Historically higher rates of vaccination have led to near eradication of cervical cancer among women in some countries. For example, in 2020 in Scotland, no new cases of cervical cancer were reported among AYA women who were vaccinated against HPV between 1988 and 1996 (388).

Environmental Risk Factors in Children and AYAs

Studies have evaluated how exposure to environmental carcinogens, specifically in children and young adults, can increase the risk of certain types of cancers.

★ SIDEBAR 16

HPV Vaccination Recommendations



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

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

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

- **Two doses of HPV vaccine**, given at least 6 months apart, for **adolescents younger than age 15** (except immunocompromised persons).
- **Three doses of HPV vaccine** for adolescents and **young adults ages 15 to 26** and for **people with weakened immune systems**.
- **Shared decision-making** through discussion with health care providers for **adults ages 27 to 45**; if an individual chooses to be vaccinated, three doses of HPV vaccine.

Source: (1).

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

GARDASIL 9

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

FDA APPROVED FOR:

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

Exposure of AYA and children to pesticides either directly through work in the agricultural industry or indirectly from wastewater, in the air, or from cohabitating with family members who work on farms, can increase the risk of developing certain types of cancers, such as childhood leukemia (389-392). Exposure to pesticides during pregnancy has been shown to increase the risk of leukemia after birth and during adolescence (393).

Parental occupations that are associated with using known carcinogens have also been associated with increasing cancer risk in children who live in the same household (394,395). One study found that occupational exposure among parents to crystalline silica, common in mining and demolition work, and/or chromium doubled the risk of childhood ALL and AML (396).

Air pollution, which is composed of fine particulate matter, has also been shown to increase mortality from cancer in children and AYAs. Certain levels of air pollution can increase cancer mortality for childhood lymphomas and central nervous system tumors as well as AYA central nervous system tumors and carcinomas (397).

Continued research into understanding the types and duration of exposures to environmental carcinogens and how these exposures increase the risk of cancers among children and AYA populations is essential.

Screening for Early Detection

IN THIS SECTION, YOU WILL LEARN:

- Cancer screening aims to detect cancer or abnormal cells that may become cancerous in people without any signs of the disease.
- The United States Preventive Services Task Force, a panel of experts in preventive medicine, periodically issues evidence-based screening recommendations for cancers of breast, cervix, colon and rectum, lung and bronchus, and prostate.
- Cancer screening is a multistep process that includes receiving the recommended test, as well as follow-up care if the initial test shows abnormal findings.
- Disadvantaged segments of the US population experience disparities in the recommended cancer screening and follow-up care.
- Evidence-based interventions are proving effective in increasing adherence to recommended cancer screening guidelines.
- Researchers are cautiously optimistic about the potential of artificial intelligence and minimally invasive screening tests in detecting cancers early.

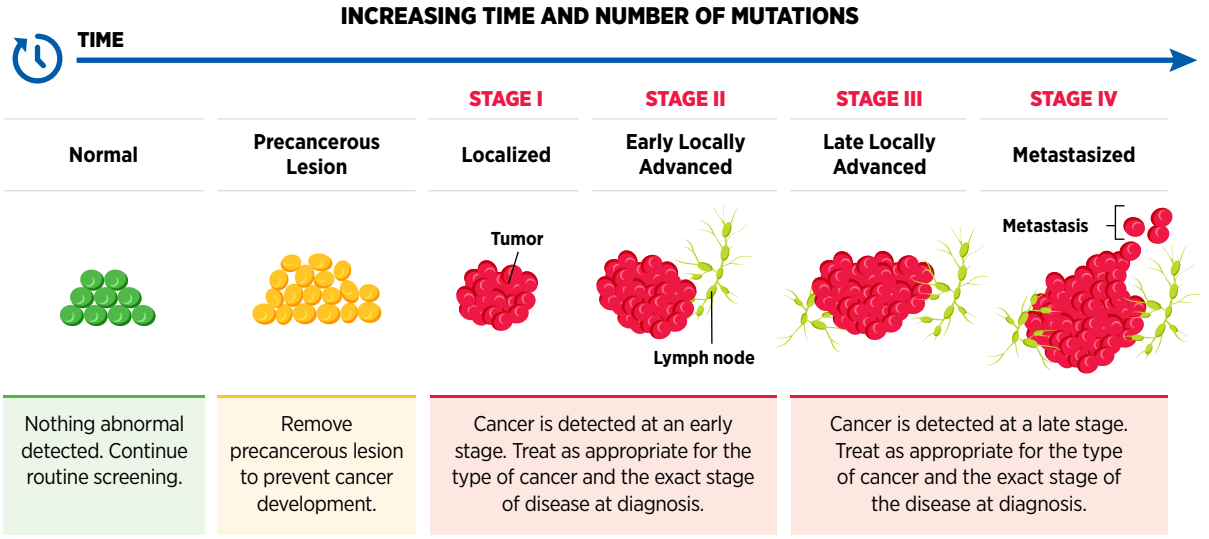
Cancer screening is the systematic process of checking for cancer or for abnormal cells that may become cancerous before a person has any signs or symptoms of the disease. The purpose of cancer screening is to detect aberrations at the earliest possible stage of cancer development. When detected early, cancer may require less aggressive treatments and may be curable. For instance, early-stage cancers are typically smaller, have not spread to other parts of the body, and can sometimes be removed completely with surgery. In contrast, cancers detected at later stages may require more complex treatments, which may be less effective and with significant side effects (see **Figure 13**, p. 64).

Importance of Cancer Screening and Follow-up Care

The overarching goal of cancer screening is to reduce the burden of the disease in the general population. Several recent studies have shown that certain forms of cancer screening can reduce deaths from specific types of cancer. Findings from a study of patients at increased risk for lung cancer showed that screening resulted in 21 percent and 39 percent reductions in deaths from any cause and from lung cancer, respectively (398). The reduction in breast cancer–related deaths in the past five decades is yet another example underscoring the importance of routine

FIGURE 13

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 as long as 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 a cure. If the test finds late-stage cancer, for example, stage III or stage IV for solid tumors, the likelihood of a cure 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.

Source: (73).

screening. A recent study reported that breast cancer mortality in the United States per 100,000 women has declined from 48 deaths in 1975 to 27 deaths in 2019 (399). Projections from the study showed that 25 percent of this reduction was attributable to breast cancer screening (399). Another study evaluating benefits of adhering to cancer screening recommendations issued by the US Preventive Services Task Force (USPSTF) (see **Guidelines for Cancer Screening**, p. 66) projected that just a 10-percentage point increase in adherence could prevent an estimated 15,580 additional deaths from lung, colorectal, breast, and cervical cancers combined (400).

According to recent estimates, **routine cancer screening has saved the US economy about $6.5 to $8.6 trillion dollars** since the introduction of the US Preventive Services Task Force recommendations in 1996.

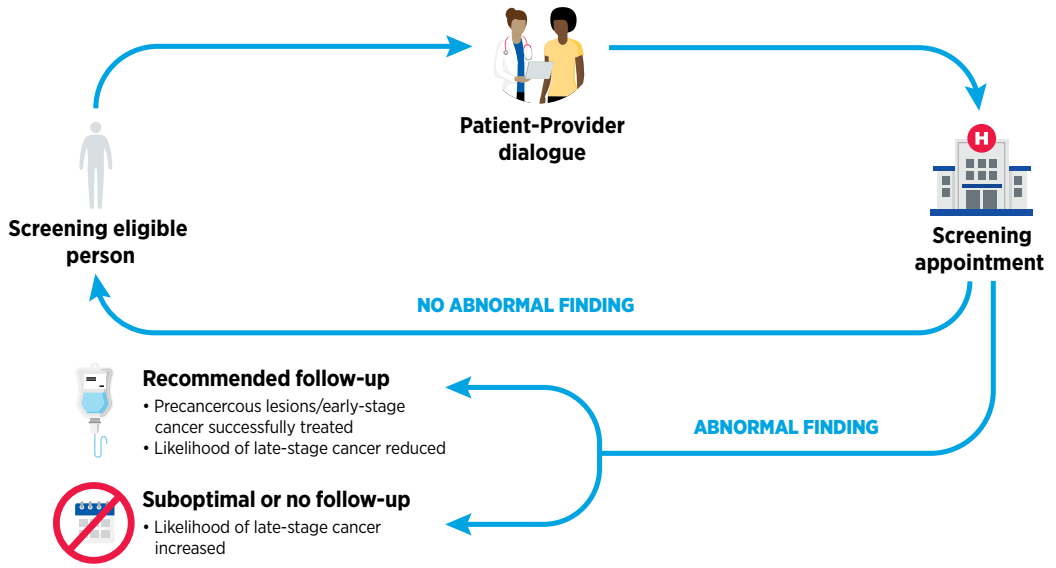
Source: (401).

W24

Cancer screening also reduces the likelihood of developing advanced-stage cancer. In a county-level population-based ecological study, researchers evaluated the impact of prostate cancer screening on the likelihood of developing advanced-stage prostate cancer. The analysis included nearly half a million responses from all US counties that were captured by the Behavioral Risk Factor Surveillance System, a system of telephone surveys conducted by the Centers for Disease Control and Prevention (CDC) to collect and collate state-level health data of US residents. Researchers found that US counties with higher rates of prostate cancer screening between 2004 and 2012 had lower incidence of advanced-stage prostate cancer and lower number of deaths from prostate cancer (402). Findings show that a 10 percent higher probability of prostate cancer screening at the county level between 2004 and 2012 was associated with a 14 percent lower incidence of advanced-stage prostate cancer between 2015 and 2019, and with a 10

FIGURE 14

Cancer Screening 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.

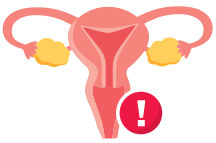
percent lower risk for prostate cancer mortality between 2016 and 2020 (402).

It is important to note that cancer screening is a continuum involving a series of tasks and steps (see **Figure 14**, p. 65). For individuals who are eligible for cancer screening, the process begins with a dialogue between individuals and their health care provider about the benefits and harms of cancer screening based on risk factors specific to them, such as a family history of cancer (see **Eligibility Criteria for Cancer Screening**, p. 66). If the initial recommended screening test indicates no abnormality, no action is needed until the next time the routine cancer screening is due. However, if the initial recommended screening test identifies precancerous lesions or presence of cancer or shows inconclusive results, follow-up care may be necessary, and the future course of action should be determined in consultation with the health care provider. For example, additional tests may be necessary to confirm initial findings, as well as to diagnose the cancer stage. Health care providers may use this information to recommend a course of treatment, ranging from surgical removal of precancerous lesions or cancer to treatment with anticancer drugs.

Unfortunately, many people do not follow up after the initial screening even when the findings indicate an abnormality (404). The reasons for suboptimal follow-up care include structural and systemic barriers, lack of transportation, not being able to take time off from work, and lack of health insurance. It is critical that people establish a regular dialogue with their health care providers about routine cancer screenings, as well as about follow-up care plans if initial findings indicate that cancer may be present. Patient navigators can be especially helpful in ensuring high degrees of follow-up by overcoming common barriers to care.

It is also important to recognize that while the benefits of routine cancer screening are many, cancer screening is a medical procedure and does carry potential harms (see **Sidebar 17**, p. 66). Experts carefully consider the risks and benefits

A modeling study of cervical cancer screening–eligible women projected that **100 percent adherence to follow-up** after an abnormal screening result could **lead to a reduction in incidence and mortality rates** by 23 percent and 20 percent, respectively.



Source: (403).

W25

SIDEBAR 17

Benefits and Potential Harms of Cancer Screening

The US Preventive Services Task Force (USPSTF) and other professional societies focused on cancer care meticulously review the available scientific evidence to weigh benefits of screening for a specific cancer type against potential harms before issuing final screening guidelines. For cancers with recommended screening guidelines, benefits of screening outweigh its potential harms:

Cancer Screening helps reduce:

LIKELIHOOD OF ADVANCED DISEASE later on in life and may help avoid complex treatment regimens.

CANCER INCIDENCE by removing precancerous lesions, which can reduce, or even eliminate, an individual's risk of ever developing screened cancer.

CANCER MORTALITY by treating precancerous lesions or cancer at an early stage of development when the likelihood of successful treatment is higher, and cure is possible in a cancer that would have otherwise caused a cancer-related death.

Cancer screening could potentially lead to:

ADVERSE EVENTS, for example, colonoscopy can potentially cause bleeding or a cut in the wall of the colon.*

INCIDENTAL FINDINGS, such as finding an unrelated medical problem, and may require follow-up tests or procedures, which also have risks.

OVERDIAGNOSIS, which is the detection of precancerous lesions or cancers that may not go on to cause symptoms and threaten life, leading to unnecessary treatment with its own potential harms.

ANXIETY, FEAR, AND/OR WORRY in individuals who are eligible for cancer screening and may not have the disease.

FALSE-NEGATIVE RESULTS in individuals who are not free from screened cancer, resulting in missed opportunities for early treatment.

FALSE-POSITIVE RESULTS in individuals who do not have the screened cancer, causing additional unnecessary medical procedures, treatments, and anxiety.

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

of cancer screening when developing the recommendations (see **Guidelines for Cancer Screening**, p. 66). Dialogue between providers and patients, as well as easily available and understandable information, about the benefits and potential harms of cancer screening can play a pivotal role for people in making an informed decision about cancer screening.

Guidelines for Cancer Screening

Panels of subject matter experts, convened by government agencies and some professional societies focused on public health, develop evidence-based recommendations for cancer screening through a careful and meticulous process. This report focuses on screening recommendations developed and issued by USPSTF, which is a congressionally mandated independent panel of experts and is convened by the Agency for Healthcare Research and Quality of the US Department of Health and Human Services. USPSTF is charged with making evidence-based recommendations that can be used in primary care settings to prevent disease, including cancer. USPSTF uses a multistep process that includes a careful review of the available evidence on the topic and engagement of the scientific community and the public before issuing the final recommendations. There are some differences in the process used by different organizations, but all organizations aim for the same rigor to ensure maximal benefit and minimal harm to public health.

Eligibility Criteria for Cancer Screening

Population-level cancer screening guidelines are developed based on a person's lifetime risk of developing cancer. People without a family history or personal history of cancer, and without an inherited genetic condition that may cause cancer, are at an average risk of being diagnosed with the disease. Two

key considerations for recommending screening in average-risk individuals are sex assigned at birth and age. People with a strong family history or a personal history of cancer, certain tissue makeup, an inherited genetic condition, or exposure to one or more cancer risk factors are at a higher-than-average risk of being diagnosed with cancer. One example is individuals who smoke, which significantly increases their likelihood of developing lung cancer and dying from it (see **Eliminate Tobacco Use**, p. 44).

Women with extremely dense breast tissue are considered at a higher-than-average risk of being diagnosed with breast cancer. Having dense breast tissue is not abnormal, but it is one of the risk factors for developing breast cancer (405). Furthermore, dense breast tissue, which appears white on a mammogram, can mask tumors, making it more challenging to detect cancer early.

People with hereditary cancer syndromes are at a higher-than-average risk of being diagnosed with cancer because of the genetic mutations they carry, which predispose them to certain types of cancer (see **Figure 6**, p. 33). For example, von Hippel–Lindau syndrome is caused by mutations in the VHL gene, which is important for regulating cellular processes in response to changes in oxygen levels within cells. People who have von Hippel–Lindau syndrome are at an increased risk of developing cancers of the kidney and brain and other parts of the nervous system. Experts recommend genetic testing and counseling for those with a hereditary cancer syndrome, including for children (see **Genetic Testing and Surveillance in Children With Cancer Predisposition**, p. 69).

Some of the factors used to determine eligibility for cancer screening, such as exposure to cancer risk factors, are different for each person and may change throughout life. It is also noteworthy that cancer screening is a process and not a single test or scan (see **Figure 14**, p. 65). It is important that people stay abreast of the most up-to-date information on cancer screening through an ongoing dialogue with their health care providers and develop a personalized cancer screening plan that considers their specific risks and tolerance of potential harms from screening tests.

Recommendations for Cancer Screening

USPSTF issues recommendations for screening for certain cancer types when the evidence indicates that the benefits of screening outweigh the potential harm, recommendations against screening for certain cancer types when the evidence indicates that the potential harm from screening outweighs benefits, as well as informs if there is insufficient evidence to make a recommendation for certain cancer types. For example, USPSTF recently concluded that the current evidence was insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adolescents and adults (406). Based on confidence in the available evidence, USPSTF assigns a grade to its final recommendations; the grade determines which services are covered without out-of-pocket costs under the Patient Protection and Affordable Care Act (ACA). USPSTF can also assign different grades to different population groups within the same cancer type (see **Sidebar 18**, p. 68). The finalized recommendations and review of the scientific evidence used to develop recommendations are published in a scientific journal and on the USPSTF website.

USPSTF periodically revises its recommendations for cancer screening as new evidence becomes available. For example, in April 2024, USPSTF revised its recommendations for breast cancer screening to lower the age to start routine screening from 50 years to 40 years (407). Furthermore, USPSTF did not find sufficient evidence to assess whether breast cancer screening for individuals 75 and older is beneficial or harmful, or whether those who have dense breasts and whose mammogram does not show any signs of cancer should undergo supplemental screening using magnetic resonance imaging (MRI) or ultrasonography (407).

The updated recommendations were based on 20 studies, including three randomized controlled screening trials, as well as on several modeling studies that also included race-specific breast cancer models for Black women, who have a 40 percent higher risk of death from breast cancer compared to White women (3,408). The revised recommendations apply to cisgender women and all other persons assigned female at birth, including transgender men and nonbinary persons (407). The reduced starting age for breast cancer screening in the revised recommendations is estimated to save 19 percent more lives from breast cancer (407,409).

Researchers are continually working to improve cancer screening, with the ultimate goal of maximizing benefits from screening while minimizing potential harms. For example, a recent study reported that for those who do not have a family history of colorectal cancer and whose first colonoscopy did not show any signs of colorectal precancerous lesions or cancer, the interval between colonoscopy screenings can be extended from 10 years to 15 years without compromising the benefits of colorectal screening (410). These findings have the potential to reduce any adverse events as well as anxiety associated with colonoscopy. Another study found that the risk of developing cervical precancerous lesions at 8 years after a negative human papillomavirus (HPV) screening test was comparable to the risk at 3 years after a negative cytology screening, which is the current standard for acceptable risk (411). The findings suggest that primary screening intervals for HPV detection may be extended safely beyond the current 5-year recommendation.

SIDEBAR 18

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
	The current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women 75 years or older.	I
CERVICAL 	Screening is recommended every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, screening is recommended every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting).	A
	Screening is not recommended in women younger than 21 years, or in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.	D
COLORECTAL 	Screening for colorectal cancer is recommended in all adults aged 50 to 75 years.	A
	Screening for colorectal cancer is recommended in adults aged 45 to 49 years.	B
LUNG 	Annual screening with LDCT is recommended in adults ages 50 to 80 who have a 20 pack-year‡ smoking history and 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 	For men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Clinicians should not screen men who do not express a preference for screening.	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, United States Preventive Services Task Force.

* Only USPSTF recommendations are included here. 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.

Tests for Cancer Screening

When developing cancer screening recommendations, USPSTF also recommends which tests should be used for different types of cancer. This information is gleaned from the available scientific evidence, and USPSTF carefully weighs the benefits and potential harms of different tests before making a final recommendation.

There are different kinds of cancer screening tests that include laboratory tests to determine the changes in cancer biomarkers in biospecimen samples, and imaging or endoscopic procedures to look for specific abnormalities (see **Sidebar 19**, p. 70).

Sometimes, additional tests beyond USPSTF recommended tests may be used based on particular situations as determined by the health care provider. For example, breast MRI is not a USPSTF-recommended test and is not typically used to screen for breast cancer. However, a breast MRI may be performed to further evaluate abnormal findings on mammograms for persons with dense breast tissue, which makes it hard to see abnormal areas on mammography (412). Furthermore, researchers continually evaluate the safety and accuracy of new and improved methods. For example, findings from a recent study showed that colorectal cancer screening based on a fecal immunochemical test (FIT) that detects three proteins in a stool sample was predicted to decrease colorectal cancer incidence by 5 percent and associated deaths by 4 percent, compared to screening based on the current standard FIT, which detects only one protein in stool sample (413).

★ SPOTLIGHT

Genetic Testing and Surveillance in Children With Cancer Predisposition

Childhood cancers are considered rare and constitute less than 1 percent of all new cancer diagnoses each year, but they are the second leading cause of death and the leading cause of disease-related death in children (414). Advances in genetic sequencing have revealed that about 10 percent to 15 percent of all childhood cancers are attributable to inherited genetic mutations that predispose children to the risk of developing certain types of cancer (154,155,157). Genetic testing and surveillance can provide a proactive approach to monitoring and managing cancer risk in children with a known predisposition to cancer. One modeling study evaluated the benefit of universal population-based genetic testing of newborns for cancer predisposition syndrome (415). The model estimated that, among a typical US birth cohort of 3.7 million newborns, 1,803 newborns would develop cancer before age 20. The model suggested that universal screening could identify 13.3 percent of newborns as at-risk, potentially resulting in a 7.8 percent decrease in cancer deaths before age 20 if these at-risk newborns are placed under surveillance (415).

Unlike recommendations for routine cancer screening in adults, cancer screening in children is more specialized and focuses on those who have hereditary cancer syndromes or show early signs or symptoms of cancer (416) (see **Table 4**, p. 71). In 2016, the American Association for Cancer Research® (AACR) convened the Childhood Cancer Predisposition Workshop, which issued its recommendations in 2017 in a series of articles for genetic testing and surveillance in children at risk of developing cancer (417-434). These recommendations provide a comprehensive framework for monitoring and managing the risk of childhood cancer.

Genetic testing in children who are at a high risk of developing cancer has many advantages. For example, early identification of genetic predispositions can allow for regular monitoring and early intervention, and can significantly improve prognosis and survival rates. Furthermore, genetic testing can help develop tailored screening and prevention strategies, leading to more effective management of cancer risk. The knowledge of genetic risk also enables informed decisions about health management, preventive measures, and lifestyle changes (441).

It is important to note that genetic testing also carries potential drawbacks and challenges. The knowledge of a genetic predisposition to cancer can cause significant anxiety and stress for both the child and their family. Concerns about the child's right to autonomy and the potential for genetic discrimination in insurance and employment are important ethical and legal considerations (442). Moreover, genetic tests are not always definitive, and false positives or false negatives can lead to unnecessary interventions or a false sense of security (441).

Parents and health care providers should discuss the benefits and potential risks of genetic testing in children for cancer, especially if there is a family history of cancer. Early detection through appropriate genetic testing for cancer predisposition and subsequent surveillance can lead to better outcomes and more effective treatment strategies for childhood cancers.

SIDEBAR 19

USPSTF-recommended Tests to Screen for Cancer

Mandated by Congress and convened by the Agency for Healthcare Research and Quality, the US Preventive Services Task Force (USPSTF) is an independent panel of experts in preventive care. USPSTF rigorously reviews 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 recommendations by USPSTF to screen for four cancer types in individuals who are at an average risk of being diagnosed with cancer and to screen for lung cancer in individuals who are at a higher-than-average risk of being diagnosed with lung cancer.

Breast Cancer

DIGITAL MAMMOGRAPHY

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

DIGITAL BREAST TOMOSYNTHESIS

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

Cervical Cancer

CYTOLOGY

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

HIGH-RISK HUMAN PAPILLOMAVIRUS (HPV) TEST

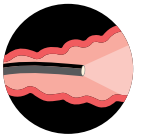
Detects the presence of certain cervical cancer–causing types of HPV and identifies people for whom further testing is recommended. It does not directly detect precancerous or cancerous cervical lesions.

Colorectal Cancer

STOOL-BASED TESTS

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

DIRECT VISUALIZATION TESTS



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

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

Lung Cancer

LOW-DOSE CT SCAN

Uses a lower dose of X-rays to rapidly image the lungs and detect any abnormalities (e.g., nodules) suggestive of lung cancer. Suspicious lesions may be biopsied to examine for abnormal or cancer cells.

Prostate Cancer

PSA TEST

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

Source: (1).

★ TABLE 4

Genetic Testing and Surveillance of Cancer Predisposition Syndromes in Children*

SYNDROME	GENE(S) TESTED	ASSOCIATED CANCERS	SURVEILLANCE GUIDELINES
Beckwith–Wiedemann Spectrum (BWS)	Multiple, including *CDKN1C*, *H19*, *IGF2*	Wilms tumor, hepatoblastoma, adrenal carcinoma	Abdominal ultrasound every 3 months until age 8; serum alpha-fetoprotein (AFP) every 3 months until age 4 (435).
Familial Adenomatous Polyposis (FAP)	*APC*, *MUTYH*	Colorectal cancer, duodenal and other gastrointestinal cancers, desmoid tumors	Annual physical examination; colonoscopy or sigmoidoscopy every 1–2 years, beginning at age 10–12, or 10 years prior to the earliest cancer diagnosis in the family; abdominal ultrasound; serum AFP for children under 5 (436).
Li–Fraumeni Syndrome (LFS)	*TP53*	Wide range of early-onset cancers, including soft tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia	Full check-up every 3–4 months, including blood pressure; growth curve (i.e., rapid height/weight gain); masculinization (e.g., pubic hair, armpit sweating, adult body odor, male-pattern baldness); neurologic assessment; for some cancers, full-body MRI (437).
Neurofibromatosis Type 1 (NF1)	*NF1*	Neurofibromas, malignant peripheral nerve sheath tumors, optic gliomas, other brain tumors	Annual physical exams; ophthalmic evaluations; MRI of the brain and spine if symptoms suggest tumors (438,439).
Retinoblastoma	*RB1*	Retinoblastoma (eye cancer), osteosarcoma; typically, in children under 5	Dedicated ophthalmic screening, with frequency of examinations adjusted on the basis of expected risk for *RB1* mutation; more frequent screening in children at high risk for retinoblastoma (440).

* This is a selected list of cancer predisposition syndromes affecting children. The indicated testing and guidance are not exhaustive and are not meant to replace clinical advice by trained health care professionals.

Suboptimal Uptake of Cancer Screening

Following the recommended cancer screening is one of the most important ways to reduce cancer burden at the population level. Unfortunately, adherence to cancer screening remains suboptimal. Furthermore, screening patterns vary for different types of cancer among racial and ethnic minority groups, citizens of sovereign Native Nations, and medically underserved populations (see **Table 5**, p. 72). As detailed in the *AACR Cancer Disparities Progress Report 2024*, there are several reasons for low rates of cancer screening and genetic testing, including social and structural barriers; bias and discrimination against marginalized populations in the health care system; mistrust of health care professionals among minoritized populations; lack of access to quality health insurance; low health literacy; and miscommunication between patients and providers (29).

It is important to fully understand whether suboptimal uptake of cancer screening and follow-up care contributes to higher burden of cancer in people belonging to certain population groups. One of the ways to improve cancer screening uptake is to deliver care that is tailored to specific populations and is designed to overcome systemic and structural barriers. Because certain populations have a higher risk of developing cancer, it is also important to develop screening guidelines and interventions that are based on data from the population for which the recommendations have been issued.

Progress Toward Increasing Adherence to Cancer Screening Guidelines

Multilevel and multipronged approaches are required to eliminate cancer inequities across the continuum of care, including improved uptake and follow-up of recommended evidence-based cancer screening among all eligible individuals. Stakeholders across the cancer care continuum are working together to achieve these goals. As detailed in the *AACR Cancer Disparities Progress Report 2024*, several evidence-based approaches have shown promising outcomes

TABLE 5

Percentage of Eligible Individuals Up to Date With USPSTF Screening Guidelines in United States in 2021

		BREAST CANCER*	CERVICAL CANCER*	COLORECTAL CANCER*	PROSTATE CANCER†	LUNG CANCER‡
Overall Screening Uptake		**75.6**	**75.5**	**71.6**	**36.3**	**16.4**
Race and Ethnicity	White	75.7	78.1	74	40.2	16.5
	Black	81.6	73.3	71.3	32.5	17.1
	Hispanic	73.8	68.7	62.1	26.7	15.7
	AI/AN	52.8	64	62.6	N/A	12.9
	Asian	66.6	63.6	60.9	17.6	23.1
Place of Residence	Large central metro	75.5	73.1	71.7	N/A	N/A
	Nonmetropolitan	72.2	72	69.3	N/A	N/A
SOGI	Straight	76	76	72.4	N/A	N/A
	Gay or lesbian	78.8	71.4	76.1	N/A	N/A
	Bisexual	60.6	69.4	70	N/A	N/A
Income	>400% FPL	81.4	83.4	78.6	76.8	14.5
	≤ 138% FPL	64.8	67.4	60.3	8.9	17.5
Education	College degree	81.4	83.8	78.4	N/A	16.6
	Less than high school	63.6	57.7	59.2	N/A	13.9
Insurance Status	Private	80.1	79.8	71.0	39.6	17.2§
	Medicare (≥65 years)	58.8	N/A	74.1	46.3	
	Uninsured	42.3	56.6	29.8	13.4	3.4
Disability	No	77	75.8	72.3	N/A	N/A
	Yes	65.8	64	71.6	N/A	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.

* Source: (443).

† Source: (444). Income thresholds are >200% of FPL and <100% of FPL.

‡ Source: (445). Income thresholds are >$100,000 and <$25,000. The data year for lung cancer screening is 2022. Numbers represent prevalence of lung cancer screening according to the 2021 USPSTF guidelines.

§ This percentage represents individuals who were insured by any type of private or public insurance.

in increasing awareness and uptake of routine cancer screening and follow-up care, as well as in reducing inequities in cancer screening (29).

The Community Guide, an evidence-based set of guidelines developed by the Community Preventive Services Task Force, recommends several approaches for both patients and providers to increasing cancer screening. These approaches include engaging community health workers; implementing multilevel interventions, such as increasing literacy about cancer screening and reducing structural barriers to cancer screening; and instituting patient navigation services. In addition, researchers are taking novel approaches to further improve uptake of the recommended cancer screening and follow-up care, some of which are highlighted below.

Using Electronic Health Records

Electronic health records (EHR) are routinely used in health care settings, including for cancer care (446). Ongoing research is showing the promise of EHR-based interventions in improving

The **United States Core Data for Interoperability Plus Cancer (USCDI+ Cancer) Program**, launched in December 2023, will define a minimum **set of key cancer-related data to be included in a person's EHR**, with the goal of improving outcomes for people with cancer through seamless sharing of health information.

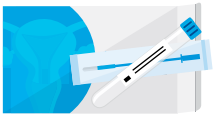
Source: (449).

W26

adherence to routine cancer screening and follow-up care. As one example, in a nonrandomized controlled trial involving 1,865 patients who were eligible for lung cancer screening, researchers evaluated the effectiveness of integrating electronic health care records into shared decision-making for lung cancer screening (447). Study was divided into a 12-month baseline period during which no intervention was applied; an 11-month period 1 in which health care professionals were prompted with preventive care reminders, and were provided with a shared decision-making software with integrated EHR and a narrative lung cancer screening guidance in the low-dose computed tomography ordering screen; and a 9-month period 2 in which in addition to the period 1 interventions, patients were sent reminders for lung cancer screening discussion and to receive lung cancer screening (447). Findings of the study show that the completion of recommended lung cancer screening care services was 16 percent before the intervention and increased to 47 percent at the end of period 2 (447).

Another study used EHR-based interventions to improve timely follow-up after abnormal breast, cervical, colorectal, and lung cancer screening results (448). The study included nearly 12,000 patients from 44 primary care practices within three health networks who had at least one abnormal cancer screening test result and had not yet followed up. Primary care practices were randomized equally into groups who provided usual care; EHR reminders; EHR reminders and outreach (a patient letter was sent at week 2 and a phone call at week 4); or EHR reminders, outreach, and navigation (a patient letter was sent at week 2 and a navigator outreach phone call at week 4). Findings show that 31.4 percent of patients who received EHR-based reminders, outreach, and navigation completed the recommended follow-up within 120 days of enrolling in the study. In comparison, 22.9 percent of patients completed the recommended follow-up in the usual care group, which did not receive any EHR-based interventions (448).

In May 2024, FDA approved two self-sampling kits for HPV to screen for cervical cancer, which allows self-collection of a vaginal sample while at a health care facility for analysis. Those who receive a positive HPV result would then continue follow-up care with a health care provider.



Source: (453).

W27

Reducing Structural Barriers

A key reason for suboptimal uptake of cancer screening and follow-up care is structural barriers, such as distance from a screening facility and lack of transportation (29). One way researchers have addressed these barriers is by mailing people kits for collecting samples for cancer screening at home. This approach has been particularly effective for improving adherence to the recommended colorectal cancer screening (450,451). Furthermore, a recent study showed that when a statewide screening program for patients who are seen at federally qualified health centers is implemented in a way that maximizes the efficiency of the program while maintaining its effectiveness, the mailed to home kits can be cost-effective, with considerable improvement in colorectal cancer screening outcomes over 5 years—preventing 91 to 98 colorectal cancers and averting 46 to 50 colorectal cancer deaths—compared with outcomes when no such program is in place (452).

Researchers are now applying this strategy to screening for other types of cancer. In a randomized controlled trial of more than 30,000 people, researchers divided individuals who were due or overdue for cervical cancer screening into groups who received usual care (i.e., patient reminders and EHR-based alerts for health care professionals), education (usual care plus educational material about screening), direct mail (usual care plus educational materials and a mailed self-sampling kit), or a choice to opt-in (usual care plus educational materials and the option to request a kit) (454). Findings show that the overall screening completion rate was the highest in the direct-mail group. Compared to those who received education alone, the screening completion rate was 14.1–16.9 percent higher in the direct-mail group among those who were due or overdue for screening (454).

Accruing evidence suggests that multilevel outreach strategies are also effective in reducing structural barriers and improving screening uptake. In a study of more than one million colorectal cancer screening–eligible individuals, researchers implemented sequential outreach, first with automated mechanisms (such as mailed prescreening notification postcards and FIT kits, automated telephone

calls, and postcard reminders), followed by personalized outreach (such as telephone calls, screening offers during office visits, and electronic messaging). Findings of this year-long study show that both automated and personalized outreach strategies substantially increased colorectal cancer screening, achieving absolute increases in screening coverage of 29 percent to 38 percent after the automated outreach and another 11 percent to 15 percent after the personalized outreach (455).

Implementing Culturally Tailored Strategies Through Community Engagement

Community engagement is an effective strategy in increasing adherence to routine cancer screening and follow-up care, especially among the medically underserved populations. Research indicates that engaging communities in a meaningful way increases awareness about the importance of undergoing routine cancer screening, participating in clinical trials, and reducing exposure to modifiable cancer risk factors (456,457). For example, interventions involving culturally tailored patient navigation significantly increase racial and ethnic minority patient engagement across the cancer care continuum and improve health outcomes (458,459).

Indigenous populations in the United States, including American Indian and Alaska Native (AI/AN) people, have higher incidence of colorectal cancer compared to other populations worldwide (36). As shown in **Table 5,** p. 72), the AI/AN populations also have lower uptake of colorectal cancer screening compared to the overall US population. Effective and culturally tailored interventions are urgently needed to increase uptake of colorectal cancer screening in these communities.

NCI's Screen to Save Colorectal Cancer Outreach and Screening Initiative is a national program launched by the NCI Center for Cancer Health Equity. The initiative aims to increase colorectal cancer screening rates among racially and ethnically diverse communities and in rural areas by providing culturally tailored, evidence-based colorectal cancer information, education, and screening resources through community health educators (461). In a recent study, researchers developed a version of the NCI Screen to Save program that was culturally tailored for the Indigenous and rural populations and, in partnership with the Indigenous and rural community outreach teams and the community advisory board, provided the tailored program to both the Indigenous and rural/suburban communities (462).

Participants who received the culturally tailored educational material successfully identified smoking and tobacco use, as well as physical inactivity, as risk factors for colorectal cancer. Furthermore, participants reported that their personal cancer screening experiences have increased their likelihood, as well as the likelihood of their family and friends, to receive routine screening for colorectal cancer. These findings highlight the importance of culturally tailored interventions through community engagement as an effective strategy for increasing screening awareness and adherence among medically underserved populations (462).

Based on findings from multiple clinical trials, **evidence-based interventions led by community health workers doubled the participation** of all racial and ethnic groups **in colorectal cancer screening programs** compared to those receiving no interventions.

Source: (460).

W28

Emerging Technologies for Early Detection of Cancer

Technological advances in genome sequencing, imaging, detection of cells and molecules in small amounts of samples, and analyses of large amounts of health data are fueling research to develop new and innovative ways to detect cancers early. Recognizing the need to evaluate emerging technologies for cancer screening, the National Institutes of Health (NIH) launched the Cancer Screening Research Network (CSRN) in February 2024 (see **Sidebar 20**, p. 75).

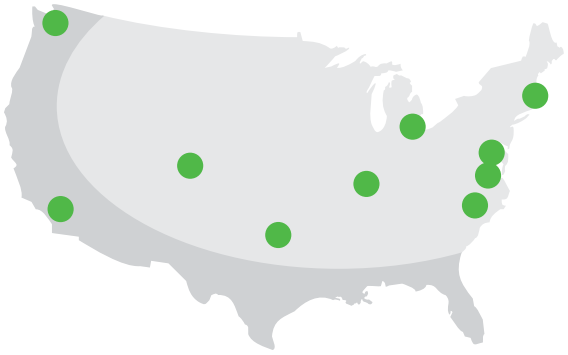
Early detection of cancer using artificial intelligence (AI)–powered devices and software and minimally invasive tests are two rapidly evolving research areas with exciting new developments. Both technologies are showing great promise in revolutionizing the cancer care continuum. For example, AI has the potential to accelerate the early detection of cancer, thus saving valuable time for patients and providers before the next course of action can be decided on if cancer is detected. Similarly, minimally invasive tests, such as liquid biopsy tests, are easier for patients, and do not require large-scale infrastructure and thus have the potential to reduce or eliminate the geographic barriers often associated with low uptake of cancer screening. Both technologies are also being tested in other aspects of the cancer care continuum, such as deciding which cancer treatment will be safe and effective for the patient and/or monitoring the patient's response to the treatment. However, both technologies also carry some drawbacks that must be carefully considered before either can be fully integrated into the standard of care (see **Sidebar 21**, p. 76).

SIDEBAR 20

The Cancer Screening Research Network

In February 2024, the National Institutes of Health (NIH) launched the Cancer Screening Research Network (CSRN), which is a network of clinical trials aimed at evaluating emerging technologies for cancer screening:

- CSRN is the **first large-scale network to focus on cancer screening**.
- CSRN **aims to conduct rigorous cancer screening** trials with large and diverse populations in a variety of health care settings.
- CSRN-**funded studies will evaluate the benefits and harms of promising new technologies** for cancer screening and determine how best to incorporate these technologies into the standard of care.
- The **ultimate goal** of the network is to **reduce cancer-related illnesses and deaths**.



- **Eight research groups from across the nation have received funding** from the National Cancer Institute (NCI), a part of NIH, to carry out the initial activities of the network.

The Vanguard Study on Multi-cancer Detection (MCD) is a pilot study conducted by CSRN to address the feasibility of using MCD tests, which can screen for several types of cancers simultaneously, in future randomized controlled trials. The study will launch in 2025 and enroll up to 24,000 people from diverse backgrounds to inform the design of a much larger randomized controlled trial. This larger trial will evaluate whether the benefits of using MCD tests to screen for cancer outweigh the harms, and whether they can detect cancer early in a way that reduces deaths.

Source: (463).

Accruing evidence suggests that the use of AI-assisted software and devices in cancer care can substantially reduce the time to make critical health-related decisions. As one example, researchers compared the performance of AI for reading mammograms to the standard method, which involves evaluation of mammograms by two independent health care professionals (464). Findings show that not only were AI-detected cancers comparable to cancers detected by trained professionals (6.1 versus 5.1 cancers detected per 1,000 screened participants, respectively), but AI-assisted software also reduced the workload, i.e., time spent by trained professionals to evaluate mammograms, by 44.3 percent (464).

Researchers are also exploring the potential of AI in early detection of cancers for which there are no screening guidelines, such as skin cancer and pancreatic cancer. For example, early detection of pancreatic cancer, which is estimated to become the second leading cause of cancer deaths in the United States by 2040 (356) and has the lowest 5-year survival rate of 13 percent (4), poses a significant challenge. Unfortunately, CT scans miss about 40 percent of small pancreatic cancers until they have advanced to a more aggressive stage (465). In a recent study, researchers developed an AI model trained on imaging data from more than 3,000 patients with pancreatic cancer for fully automated cancer detection, including small and otherwise difficult-to-detect tumors (466). The model helped discriminate visually imperceptible cancerous lesions from normal-appearing pancreases 438 days before the clinical diagnosis, a significant improvement over standard methods (466). Other recent studies have shown similar promise of AI-assisted early detection of this devastating cancer type (467).

The potential of AI in medicine is also reflected by the FDA approval of numerous AI-assisted software systems for early detection of cancer in recent years (see **Table 6**, p. 77). As the applications of AI in cancer science and medicine, including in early detection of cancers, are rapidly evolving, it is important to consider the ethical ramifications of the technology, as well as its potential to exacerbate cancer inequities (see **Sidebar 21**, p. 76) (468).

Liquid biopsy procedures are minimally invasive and can detect abnormal cells and/or other materials from tumors, such as small pieces of DNA, RNA, or proteins, that are circulating in the blood. Liquid biopsy–based tests that can detect multiple types of cancer simultaneously are called multicancer detection (MCD) assays or multicancer early detection tests. Liquid biopsy approaches are already in routine use for making treatment decisions and/or monitoring if cancer has returned

SIDEBAR 21

Artificial Intelligence and Liquid Biopsy: New Frontiers in Early Detection of Cancer

Emerging technological advances, such as artificial intelligence (AI) and minimally invasive tests (e.g., liquid biopsy), are showing great promise to revolutionize early detection of cancer. However, these technologies also carry potential drawbacks. Below are the promises they hold for advancing early detection of cancer as well as potential drawbacks that require careful consideration before these technologies are implemented in routine practice.

ARTIFICIAL INTELLIGENCE (AI) is the ability of a computer to perform tasks commonly associated with human intelligence, such as how to act, reason, and learn.

Promise of AI

ARTIFICIAL INTELLIGENCE CAN HELP...

- **Accelerate cancer early detection** through increased speed and accuracy.
- **Recognize precancerous lesions** in imaging data from screening faster and more effectively that may be missed by trained professionals.
- **Reduce the workload** (i.e., the time it takes for a team of trained health care professionals to evaluate screening results) associated with cancer screening and follow-up care.
- **Optimize electronic health records–based interventions** by integrating screening test results with reminders for the providers and patients for follow-up care if the initial screening test shows abnormality.

Potential Drawbacks

ARTIFICIAL INTELLIGENCE MAY...

- **Perpetuate data biases** if datasets used to train AI algorithms do not include diverse populations.
- **Inherit algorithmic biases** if the design choices are made by teams of professionals who do not have diverse perspectives, voices, and experiences.
- **Promote cultural bias** if algorithms are not developed carefully to consider linguistic diversity and cultural norms, among other factors.
- **Increase cancer disparities** if not made equitably accessible to all populations as well as to all health care systems, including public hospitals.

LIQUID BIOPSY is a minimally invasive test that can detect cancers from a variety of materials (such as cells and small pieces of DNA, RNA, or proteins), shed by precancerous lesions and tumors, in blood, urine, or other body fluids.

Promise of Liquid Biopsy

LIQUID BIOPSY TESTS CAN HELP...

- **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, because these tests are minimally invasive.
- **Overcome certain structural barriers**, such as geographic accessibility, because they do not require large-scale infrastructure and can be performed at a local clinic.

Potential Drawbacks

LIQUID BIOPSY TESTS MAY...

- **Lead to higher rates of false positive findings and unnecessary follow-up procedures** when used to detect multiple cancers. Follow-up procedures can be costly and invasive with their own side effects and may increase anxiety for patients and strain for health care systems.
- **Not capture early-stage cancers** or precancerous lesions as efficiently as advanced cancers.
- **Not yield the same benefits for all populations** if racial and ethnic minority populations are not well represented in the research leading to the development of such tests.
- **Be out of reach for many** minoritized and medically underserved populations because of costs and access.

Source: (29).

in patients who have already received cancer treatment (469,470). Because these approaches are minimally invasive, they can be especially beneficial for children and older adults with cancer (471). During the 12-month period covered by this report (July 2023–June 2024), FDA has also approved two minimally invasive tests for early detection of cancers or determining cancer risks among those who are genetically predisposed (see **Sidebar 22**, p. 77).

TABLE 6

A Selected List of AI-assisted Medical Devices and Software for Early Cancer Detection Approved by FDA During July 2023–June 2024*

NAME OF SOFTWARE/ DEVICE	TYPE OF CANCER SCREENING	WHAT IT DETECTS	APPROVED IN
MAGENTIQ-COLO	Colorectal cancer	Detects precancerous lesions in real time	July 2023
Transpara Density 1.0.0	Breast cancer	Analyzes breast density to aid in cancer detection	December 2023
autoSCORE	Various cancers	Supports diagnosis by scoring cancer risk in images	January 2024
DermaSensor	Skin cancer	Detects skin lesions including melanoma, basal cell carcinoma, and squamous cell carcinoma	January 2024
LungQ v3.0.0	Lung cancer	Analyzes lung nodules for malignancy	January 2024
HealthFLD	Various cancers	Uses AI for lung cancer screening and other thoracic abnormalities	February 2024

AI, Artifical Intelligence; FDA, US Food & Drug Administration.

* This list is not exhaustive. A complete list of FDA-approved AI-assisted software and devices can be found at: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

SIDEBAR 22

FDA-approved Minimally Invasive Tests for Early Cancer Detection or Risk Reduction

The potential of minimally invasive tests in early cancer detection in clinical practice is underscored by recent approvals by the US Food and Drug Administration (FDA) between July 2023 and June 2024, the time period covered by this report:

The Invitae Common Hereditary Cancers Panel

Approved in September 2023, to assess the risk of hereditary cancers, such as those associated with Lynch syndrome. The test analyzes a person's blood sample for changes in 47 genes that are linked to hereditary cancers (472).

ColoSense

Approved in May 2024, to screen for colorectal cancer. The test, also called multitarget stool RNA test, analyzes stool sample for the presence of RNA molecules associated with colorectal cancer as well as a product of blood (473,474).

Liquid biopsy tests are showing promise in detecting cancer types for which there are no population-based screening guidelines. As described above, pancreatic cancer poses a serious challenge to public health because of low survival rates and lack of effective strategies to detect it at early stages of development. It is encouraging that researchers have developed a blood test to accurately detect early-stage pancreatic cancer, according to results from a large study that included nearly 1,000 people from several countries (475). The test analyzed small pieces of RNA shed by tumors into the bloodstream in combination with a test that detects a protein called CA19-9, which is a marker for pancreatic cancer. The findings show that the combination accurately identified 97 percent of people with early-stage pancreatic cancer (475,476).

Liver cancer has a high mortality rate, with nearly 30,000 deaths estimated to occur in the United States in 2024 alone (4).

Furthermore, the 5-year survival rate from the disease is only 22 percent, which can increase to more than 70 percent if the cancer is detected early (4). However, current tests available to monitor people at high risk of developing liver cancer, such as those with hepatitis B virus infection, do not work well, are not readily available to those who need them, and are expensive. In a new study, researchers used an AI-assisted model to identify small pieces of DNA shed by liver tumors, and then used this knowledge to develop a liquid biopsy test for early detection of liver cancer (477). Findings show that the test reliably identified patients with liver cancer, including early-stage disease, in blood samples from hundreds of people (477).

Although the examples discussed here are encouraging, researchers are calling for large-scale randomized controlled trials to ensure that these tests will improve health outcomes and extend lives for patients, while minimizing cost and unintended adverse effects (478).

Inspiring Science. Fueling Progress. Revolutionizing Care.

IN THIS SECTION, YOU WILL LEARN:

- Researchers are harnessing knowledge of the cellular and molecular underpinnings of cancer initiation and progression to develop safer and more effective treatments for patients.
- Advances in novel and innovative approaches to surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—the five pillars of cancer treatment—are saving and improving lives.
- From July 1, 2023, to June 30, 2024, the US Food and Drug Administration (FDA) has approved 15 new anticancer therapeutics, a new imaging agent to aid breast cancer surgery, and has expanded the use of 15 previously approved anticancer therapeutics to treat additional cancer types.
- Included in the FDA approvals are the first tumor-infiltrating lymphocyte-based cellular immunotherapy that will benefit patients with melanoma, a new bispecific antibody against a novel target for patients with small-cell lung cancer, the first KRAS-targeted therapy for colorectal cancer, and several new molecularly targeted therapeutics and immunotherapeutics for the treatment of patients with different types of blood cancer.
- While these exciting new advances have the potential to transform patient care, much work is needed to ensure equitable access to these treatments for all populations.

Progress across the continuum of cancer science and medicine improves survival and quality of life for people in the United States and around the world. In the United States, the overall cancer death rate is declining steadily, and more individuals are living a longer and fuller life after a cancer diagnosis (see **Cancer in 2024**, p. 11)(3). This progress is attributable, in part, to the rapid strides that we are making in cancer treatment propelled by breakthroughs in clinical research.

Clinical Research

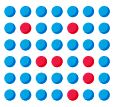
Decades of research in basic and translational sciences have deepened our understanding of the fundamental underpinnings of cancer initiation, evolution, and progression and led to the identification of numerous targets that drive cancer development (see **Understanding the Path to Cancer Development**, p. 26). After a potential target is identified and is deemed suitable for therapeutic intervention, it takes many more years of preclinical

SIDEBAR 23

Therapeutic Development

Target validation

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

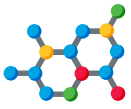


Drug screening

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

Lead identification

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



Lead optimization

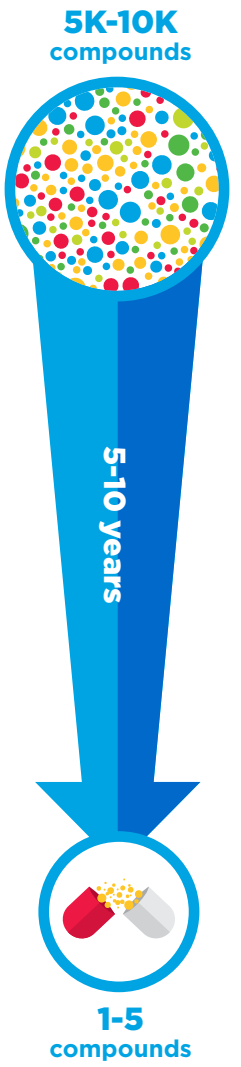
The characteristics of lead compounds are optimized to enhance potency and drug-like properties and to reduce side effects by enhancing specificity.

Preclinical testing

Optimized lead compound(s) are tested in cell-based and animal models for effectiveness, potential toxicity, optimal starting dose, and dosing schedule for clinical or "first-in-human" testing. The final compound(s) are considered 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: (1).

research before a candidate agent is developed and ready for testing in clinical research, also known as clinical studies or clinical trials (see **Sidebar 23**, p. 80).

Clinical trials evaluate 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 benefits to participating in a clinical trial. These include access to potentially more effective treatments with carefully standardized monitoring before they are widely available, a direct contribution to lifesaving cancer research, and an active involvement in making health care decisions (479). While there is some evidence that clinical trial participants may have better outcomes compared to nonparticipants, understanding whether participating in a cancer clinical trial can improve long-term survival is a topic of ongoing debate (480,481).

There are several types of cancer clinical trials, including prevention trials, screening trials, treatment trials, and supportive or palliative care trials, each designed to answer different research questions (see **Sidebar 24**, p. 81). Clinical studies in which participants are randomly assigned to receive an experimental treatment or standard of care treatment are called randomized clinical trials and are considered the most rigorous.

Clinical trials evaluating potential new therapeutics for cancer have traditionally been done in three successive

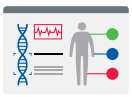
SIDEBAR 24

Types of Clinical Trials

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

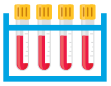
Prevention trials

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



Screening trials

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



Diagnostic trials

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

Treatment trials

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

Quality of life trials

Designed to examine whether patients with cancer can improve their quality of life by taking certain actions, such as attending support groups or exercising more. Also known as supportive care or palliative care trials, these studies evaluate the effects of certain cancer medications and treatments on quality of life and identify ways to help patients who are experiencing symptoms related to cancer and its treatments.

Natural history or observational studies

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

Correlative studies

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

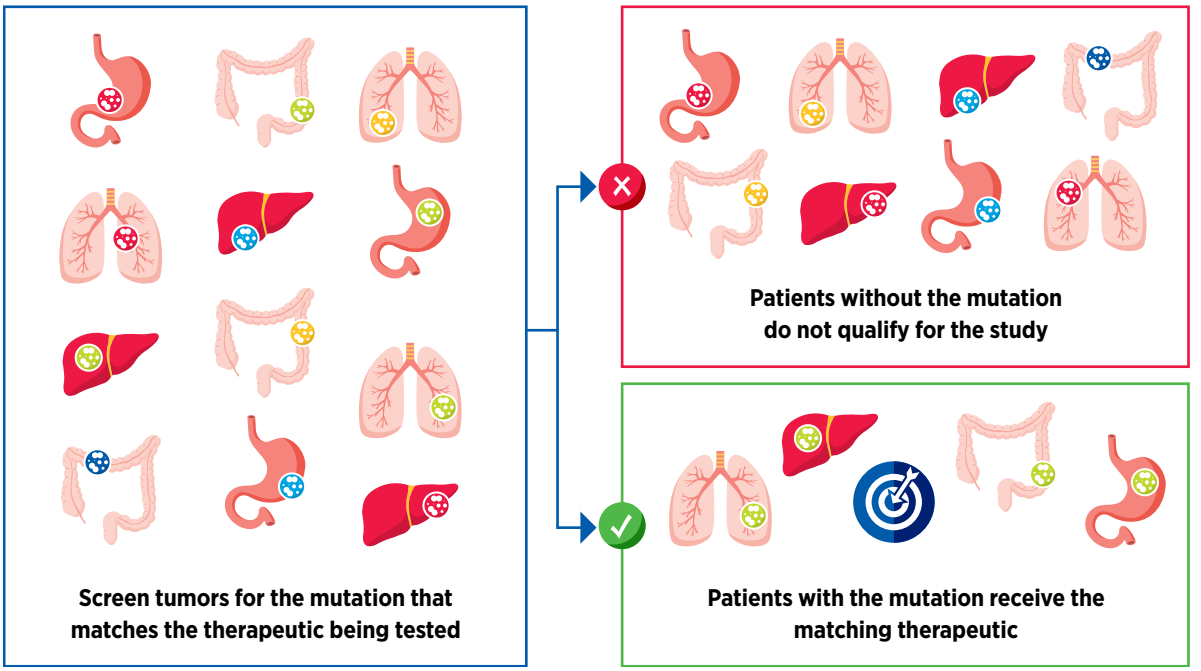
phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how humans process it, and potential toxicities. Historically, phase I trials were not designed to evaluate efficacy of a therapeutic in treating cancer. However, because of rapid progress in clinical trial design and conduct, phase I trials are increasingly incorporating a preliminary evaluation of efficacy (482). 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 (483).

Phase II studies are designed to determine the initial efficacy of an investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care; when successful, the results of these trials can be used by the US Food and Drug Administration (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.

FIGURE 15

Biomarker-guided Clinical Trial Design

BASKET TRIALS



Recent advances in our understanding of the genetic, epigenetic, and other biological drivers of cancer have led to novel ways of designing and conducting clinical trials. One of the new approaches is to use a master protocol to answer multiple questions within a single overall clinical trial. Basket trials are one type of master protocol clinical trial. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, colon, and stomach cancers. This approach allows the clinical testing of new anticancer therapeutics to be streamlined because the therapeutic is matched with the right patients at the start of the trial. This precision approach reduces the number of patients who need to be enrolled in the trial and decreases the length of time it takes for a new anticancer therapeutic to be tested and made available to patients if the trial shows it is safe and effective.

The multiphase clinical testing process requires many patients and takes years to complete (484,485). Identifying and implementing more efficient clinical development strategies are areas of extensive investigation. As one example, researchers often combine different phases into one clinical trial (labeling depends on the phases combined, e.g., phase I/II or phase III/IV clinical trials), which allows research questions to be answered more quickly or with fewer patients. Additionally, a deepened grasp of the underpinnings of cancer biology has enabled researchers to develop more effective approaches to designing and conducting clinical trials such as those evaluating treatments based on a cancer's genetic drivers rather than site of origin.

Among the new concepts and designs for clinical trials that have emerged in recent years are the basket, umbrella, and platform trials designs as part of a master protocol framework (see **Figure 15**, p. 82) (486). Master protocol, also known as main protocol, refers to an overarching trial design that can assess multiple clinical hypotheses with the goal of improving efficacy and streamlining therapeutic development. 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.

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. Umbrella studies aim to identify the best

ONLY 7.1%

Between 2013 and 2017, the **national estimate for participation of patients in cancer treatment trials** was 7.1 percent.

Source: (489).

W29

therapy for different types of genetic mutations all within the same anatomic cancer type. 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.

As our understanding of cancer biology continues to evolve and we uncover some of the most elusive questions in cancer medicine (see **Cancer Development: Integrating Knowledge**, p. 41), clinical trial designs will need to evolve as well. Additionally, the design and conduct of clinical cancer research need to keep pace with the new wave of technological advances. Novel trial designs that leverage emerging approaches, such as comprehensive tumor profiling (e.g., of genome, transcriptome, proteome, microbiome, and metabolome, among others), real-world evidence and data, as well as inputs from patient advocacy communities and social media platforms, will be pivotal to advancing the frontier of cancer clinical trials (487).

In addition, artificial intelligence (AI)–based strategies are being harnessed to further improve clinical research. Using data from multiple sources, including past clinical trials, tumor profiles, clinical data, and electronic health records from hospital systems, researchers are training AI algorithms to identify patients who are most likely to respond to an investigational therapeutic, simulate an investigational compound's mechanism of action, or potentially even create virtual trial participants referred to as digital twins of human patients seen in the clinic (488). Researchers hope that such AI-driven approaches will help bypass the greatest barrier, the low rates of patient participation, in the conduct of clinical research. However, as with all other applications of AI, careful consideration should be given to ensure equitable benefits of these emerging approaches for all patient populations.

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 25**, p. 84). Low participation in clinical trials means that many trials fail to enroll enough patients to draw meaningful conclusions about the effectiveness of the anticancer therapeutic being tested. Lack of diversity in clinical studies means that the trial participant population does not match the actual national demographics of the cancer burden under study (490). Diversity of participants is critical because the efficacy and safety of an intervention may differ among populations, e.g., among different racial and ethnic groups or between men and women. Underrepresentation in clinical trials compromises the applicability of the trial findings to the entire US 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 investigated the existing barriers that limit participation of racial and ethnic minorities and other medically underserved populations in cancer clinical trials. These studies have identified a range of factors, such as lack of awareness of clinical trials, financial challenges, limited health literacy, inadequate or complete lack of insurance, medical distrust, implicit biases among health care providers, lack of trial availability, and narrow eligibility criteria, among others (497). Many of these barriers operate at individual, systemic, and societal levels (498).

As discussed in detail in *AACR Cancer Disparities Progress Report 2024* (29), increased knowledge of the barriers to clinical trial accrual is helping researchers, regulators, and policymakers design and implement evidence-based adaptations that can improve access of potential participants to clinical research. Interventions aimed at addressing social determinants of health (see **Figure 3**, p. 21), modernizing trial design to ease patient participation, expanding eligibility criteria, improving the efficiency of data collection, including patient reported outcomes (PRO), and engaging in community outreach and patient navigation are being evaluated. Additionally, a critical area of focus for all stakeholders in medical research is fostering greater diversity, equity, and inclusion within the clinical research workforce so that it resembles the patient populations it serves.

In a recent survey of cancer clinical trial researchers and patient advocates, **participants most often rated quality of life as the top priority alongside access to care,** and toxicities, emphasizing the **importance of patient-centered research**, such as including patient reported outcomes (PROs), in clinical trials.

Source: (499)

W30

SIDEBAR 25

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:

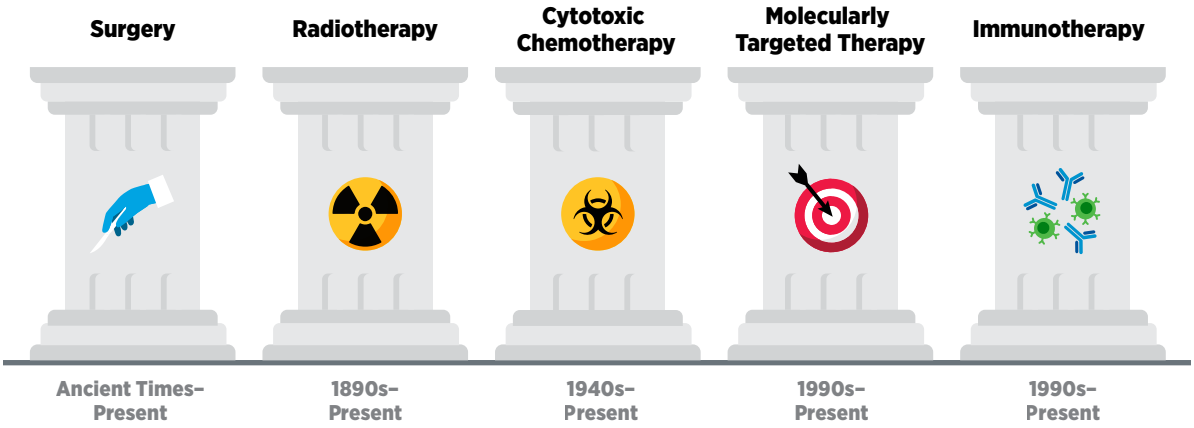
Only 2.6% and 8%	**UNDERREPRESENTATION OF RACIAL AND ETHNIC MINORITIES** The US Food and Drug Administration approval of elacestrant for patients with breast cancer in January 2023 was based on a clinical trial whose participants were mostly White (88.4 percent). Only 2.6 percent and 8 percent of participants were Black and Hispanic, respectively (491).
Consistently LESS LIKELY	**PROXIMITY TO TRIAL SITES** American Indian or Alaska Native patients with cancers of the breast, colon, lung, pancreas, and prostate are consistently less likely to live within 30 miles of a clinical trial site, compared to patients from other racial or ethnic groups (492).
67% less likely	**SOCIAL VULNERABILITY** Most socially vulnerable counties are 67 percent less likely to have any cancer clinical trials available, compared to the least socially vulnerable counties (493).
SEVERELY underrepresented	**UNDERREPRESENTATION OF GENDER MINORITIES** Gender minorities are severely underrepresented in breast cancer clinical trials (494).
68% less likely	**MINORITY-SERVING HOSPITALS** Among patients with gastrointestinal cancers, those treated at minority-serving hospitals (MSH)—facilities that predominantly provide health care to minority patients—are 68 percent less likely to enroll in a clinical trial, compared to those treated at a non-MSH hospital (495).
17% vs. 46%	**ADOLESCENTS AND YOUNG ADULTS** Analysis of a multicenter clinical trial of adolescent and young adults (AYAs) with acute lymphoblastic leukemia (ALL) showed that only 17 percent of participants were Hispanic (496), even though 46 percent of newly diagnosed US AYA patients with ALL are Hispanic.

US lawmakers and FDA are working on legislation and guidelines intended to increase the diversity of clinical trial participants (see **Diversifying and Decentralizing Trials**, p. 160) (29). 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 of new drugs (500).

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 (24). 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 or imaging facilities accessible to patients, have offered a blueprint of success to further revise and reform clinical trials and the drug approval process for the benefit of all patients with cancer. Ongoing research must continue to evaluate the impact of these approaches on advancing our nation's clinical cancer research efforts (501).

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 (504). In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar (505). The foundations for the third treatment pillar—cytotoxic chemotherapy—were established in the early 1940s, with the use of a derivative of nitrogen mustard to treat lymphoma (506). These three pillars—surgery, radiotherapy, and cytotoxic chemotherapy—continue to be critical components of cancer treatment. Introduction of the first molecularly targeted therapeutics in the late 1990s led to the establishment of the fourth pillar, molecularly targeted therapy (507). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (508). 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.

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. FDA 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. 28) 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 cytotoxic chemotherapies, all of which continue to be the mainstays of clinical cancer care (see **Figure 16**, p. 85). In recent years, there has been a rapid proliferation of molecularly targeted therapeutics and immunotherapeutics, the two newest pillars of cancer treatment, ushering in an era of personalized cancer medicine (see **Figure 16**, p. 85). Additionally, researchers are continually evaluating new ways to refine the use of surgery, radiotherapy, and cytotoxic chemotherapeutics to improve survival and quality of life for patients.

As one example, since most prostate cancers grow slowly, active monitoring has been shown to be a safe management strategy for avoiding overtreatment and preventing undertreatment. In fact, evidence is emerging that active monitoring of the disease in patients with early-stage prostate cancer is a safe alternative to receiving immediate surgery or radiotherapy (502). These findings are hopeful for patients who opt for active monitoring to avoid treatment-related adverse effects, such as sexual and incontinence problems. Similar observations have been noted among patients with certain types of thyroid cancer. Active monitoring of disease and surgery only after suspected progression has been shown to be associated with similar outcomes that are seen in patients undergoing immediate surgery (503).

The following sections focus on the recent advances across the five pillars of cancer treatment, in particular, the 15 new anticancer therapeutics approved by FDA in the 12 months spanning this report, July 1, 2023, to June 30, 2024 (see **Table 7**, p. 86 and **Supplementary Table 1**, p. 200). During the same timeframe, FDA approved 15 previously approved anticancer

TABLE 7

Newly FDA-approved Anticancer Agents: July 2023–June 2024

TYPE OF TREATMENT	GENERIC NAME	TRADE NAME	WHAT IS IT?	APPROVED FOR?
Surgery Chemotherapy Radiotherapy	pegulicianine	Lumisight	Imaging agent	Certain type of breast cancer
	melphalan	Hepzato kit	Chemotherapeutic	Uveal melanoma that has metastasized to liver*
Molecularly Targeted Therapy	adagrasib†	Krazati	Cell-signaling inhibitor	Certain type of colorectal cancer*
	belzutifan	Welireg	Cell-signaling inhibitor	Certain type of kidney cancer*
	capivasertib and fulvestrant†	Truqap and Faslodex	Cell-signaling inhibitor	Certain type of breast cancer
	eflornithine	Iwilfin	Cell-signaling inhibitor	Certain type of neuroblastoma*
	encorafenib with binimetinib†	Braftovi and Mektovi	Cell-signaling inhibitor	Certain type of lung cancer*
	fam-trastuzumab deruxtecan-nxki†	Enhertu	Antibody-drug conjugate	HER2-positive solid tumors*
	fruquintinib	Fruzaqla	Angiogenesis inhibitor	Certain type of colorectal cancer
	imetelstat	Rytelo	DNA repair inhibitor	Myelodysplastic syndromes
	ivosidenib†	Tibsovo	Epigenome-modifying agent	Myelodysplastic syndromes*
	momelotinib	Ojjaara	Cell-signaling inhibitor	Myelofibrosis
	niraparib and abiraterone acetate†	Akeega	DNA repair inhibitor	Certain type of prostate cancer*
	nirogacestat	Ogsiveo	Cell-signaling inhibitor	Desmoid tumors
	pirtobrutinib	Jaypirca	Cell-signaling inhibitor	Certain types of lymphoma*
	quizartinib†	Vanflyta	Cell-signaling inhibitor	Certain type of leukemia
	repotrectinib	Augtyro	Cell-signaling inhibitor	NTRK-positive solid tumors and certain lung cancers
	tovorafenib	Ojemda	Cell-signaling inhibitor	Certain type of glioma
	zanubrutinib	Brukinsa	Cell-signaling inhibitor	Certain types of lymphoma*
Immunotherapy	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of endometrial cancer*
	elranatamab-bcmm	Elrexfio	Bispecific antibody	Multiple myeloma
	epcoritamab-bysp	Epkinly	Bispecific antibody	Certain type of lymphoma*
	lifileucel	Amtagvi	Tumor infiltrating lymphocyte	Melanoma
	lisocabtagene maraleucel	Breyanzi	CAR T-cell therapy	Certain types of lymphoma*
	nogapendekin alfa inbakicept-pmln	Anktiva	Immune system modifier	Certain type of bladder cancer
	pembrolizumab	Keytruda	Immune checkpoint inhibitor	Biliary tract cancer*
	talquetamab-tgvs	Talvey	Bispecific antibody	Multiple myeloma
	tarlatamab-dlle	Imdelltra	Bispecific antibody	Certain type of lung cancer
	tislelizumab-jsgr	Tevimbra	Immune checkpoint inhibitor	Certain type of esophageal cancer
	toripalimab-tpzi	Loqtorz	Immune checkpoint inhibitor	Nasopharyngeal carcinoma

* New cancer type approved 2023–2024.

† Requires a companion diagnostic.

Listed are the new anticancer therapeutics approved by FDA and previously approved anticancer therapeutics that were approved by FDA for treating additional types of cancer.

therapeutics 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 on all anticancer therapeutic approvals can be found on FDA's website (https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-

SIDEBAR 26

Disparities in Cancer Treatment

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

LESS likely	**GUIDELINE-ADHERENT TREATMENT** Compared to Non-Hispanic White patients, non-Hispanic Black patients with breast cancer are less likely to receive guideline-adherent treatments, regardless of economic or residential segregation (513).
MORE likely	**DECLINE TREATMENT** Compared to White patients with breast cancer, American Indian or Alaska Native and Asian or Pacific Islander patients are more likely to decline surgery and chemotherapy (514).
LONGER times	**TIME TO TREATMENT** Compared to non-Hispanic patients, Hispanic patients with rectal cancer experience longer times to surgery (94 vs. 79 days), radiation (65 vs. 56 days), and chemotherapy (56 vs. 48 days) (515).
Significantly LESS LIKELY	**MINORITY-SERVING HOSPITALS** Minority-serving hospitals (MSH)—facilities that predominantly provide health care to minority patients—are significantly less likely to deliver therapy that is considered the best option for a patient across all cancer types compared to non-MSH hospitals (516).
Significantly LESS LIKELY	**SOCIOECONOMIC STATUS** Compared to patients with early-stage liver cancer belonging to high socioeconomic status (SES), patients from low SES are significantly less likely to receive curative treatments (517).
Significantly LESS LIKELY	**MULTIDISCIPLINARY CARE** Compared to urban patients, rural patients with prostate cancer are significantly less likely (41 percent vs. 48 percent) to receive multidisciplinary consultation for their clinical care (518).
Significantly LESS LIKELY	**GENETIC TESTING** Patients with ovarian cancer without health insurance are significantly less likely to complete genetic testing compared to those with private insurance (23 percent vs. 47 percent) (519). Genetic testing for targetable alterations is key for receiving molecularly targeted therapeutics.

notifications). 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. The fast pace of approval and increasing clinical use of these cutting-edge therapeutics warrant close monitoring of patients receiving these novel 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 receive the standard of care recommended for the type of cancer with which they have been diagnosed and the stage of cancer at the time of diagnosis (see **Sidebar 26**, p. 87). Disparities in cancer treatment are driven largely

by socioeconomic and structural factors such as lack of health insurance or of access to health care facilities as well as high costs of cancer care. Research has shown that racial disparities in survival for several cancer types can be eliminated when all patients have equivalent access to standard treatments (29). 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 (509).

Medicaid expansion through the Patient Protection and Affordable Care Act (ACA) has been shown to increase insured status, early diagnosis, and timely cancer treatment, and improve outcomes leading to reduced cancer disparities. As one example, a recent study evaluated the association between Medicaid expansion and time to breast cancer surgery and found that Medicaid expansion led to a significant reduction of disparity in surgery delays between White patients and patients from racial and ethnic minority populations (510). Additionally, Medicaid expansion has been shown to reduce racial disparities in time to chemotherapy initiation between White patients with early-stage breast cancer and those belonging to racial and ethnic minority groups (511). It is imperative that all stakeholders committed to driving progress against cancer work together to ensure equitable access to quality cancer care.

Educating health care providers about the approval processes for relevant medical products is critical if they are to adequately 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 and 17 percent of respondents reported moderate or better understanding of FDA's drug and medical device approval processes, respectively (512).

Advances in Cancer Treatment With Surgery

For centuries, surgery was the only pillar of cancer treatment (see **Figure 16**, p. 85). 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 27**, p. 89).

Sometimes, additional therapy is given before, after, or around the time of surgery based on specifics of a patient's situation (see **Sidebar 28**, p. 90). 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 (520).

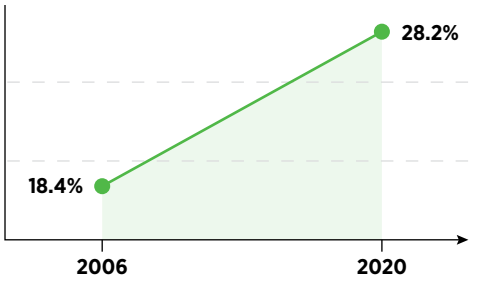
Performing Less Invasive Cancer Surgery

Several recent studies have shown that less invasive surgeries—or avoiding surgeries altogether—may benefit certain patients by minimizing postprocedural complications without compromising and sometimes improving long-term outcomes (521-524). A few examples of such findings are discussed below.

For breast cancer patients undergoing surgical resection, in addition to removing the breast tissue, surgeons often also remove what is called the sentinel lymph node, which is the first lymph node(s) to which the cancer is most likely to spread. Sentinel lymph node biopsy (SLNB) is a routine procedure during which the sentinel lymph node is identified, removed, and examined to determine whether cancer cells are present. Detection of cancer cells in sentinel lymph nodes through SLNB has been a standard of breast cancer care because it determines the extent of the disease and provides information that is central to the development of a patient's treatment plan.

Historically, researchers believed that removing the axillary lymph nodes, which are the lymph nodes that run from the breast tissue into the armpit, could reduce the risk of metastases and cancer recurrence. Therefore, all axillary lymph nodes adjacent to the affected breast were removed in a surgery known as the axillary lymph node dissection (ALND). However, ALND is an invasive procedure associated with its own morbidity, particularly lymphedema, which causes swelling in the arms that can cause pain and problems in functioning (see **Challenges Faced by Survivors**, p. 130).

Research shows that in the United States the **rate of organ preservation for rectal cancer patients** with a complete response to neoadjuvant therapy **increased from 18.4 percent in 2006 to 28.2 in 2020**.



As of 2023, **national guidelines recommend a watch and wait approach**, instead of surgical removal of the rectum, for this patient population.

Source: (529).

W31

SIDEBAR 27

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 the inside of the body onto a monitor, which allows the surgeon to see what is happening. Special surgery tools are inserted through other small cuts to remove the tumor and some healthy tissue.

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

More recently, studies have shown that ALND is not associated with any survival benefit compared to SLND and could thus be omitted for certain patients. Findings from a recent clinical trial suggest that patients whose breast cancers are 2 centimeters or smaller and whose axillary lymph nodes appear normal on ultrasonography can be safely spared SNLB without compromising their outcomes (525).

Another group for whom ALND could be omitted is patients with breast cancer who have an excellent response to chemotherapy given before surgery (neoadjuvant therapy) (see **Sidebar 28**, p. 90). In a recent study, researchers found that patients with lymph node–positive breast cancer who no longer had any signs of cancer in their nodes following neoadjuvant chemotherapy rarely experienced cancer recurrence in their axillary nodes even without undergoing ALND (526). These findings support the omission of ALND in this patient population.

Additionally, certain patients with breast cancer can safely forgo ALND if they have no signs of metastasis in the axillary lymph nodes, as determined by a negative clinical examination of the axilla; have received guideline-adherent adjuvant treatments and radiation therapy, and in whom SLNB had revealed only one or two metastases. Evidence supporting this approach was obtained from a randomized clinical trial, in which breast cancer patients with the above characteristics had similar 5-year recurrence-free survival irrespective of whether they received ALND (527).

Another patient population for whom less extensive surgery could be a safe and effective alternative are those with early-stage cervical cancer. Traditionally, most patients are treated with a radical hysterectomy, which involves removing the uterus, cervix, part of the vagina, and ligaments and tissues around the uterus. In contrast, a simple hysterectomy is a limited surgical procedure involving the removal of the uterus and the cervix.

SIDEBAR 28

Commonly Used Terms and Benchmarks in Clinical Studies

Search...

Adjuvant therapy

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

Complete response

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

Duration of response

Time from documentation of disease response to disease progression.

Median survival

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

Neoadjuvant therapy

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

Objective response rate

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

Overall response rate

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

Overall survival

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

Placebo

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

Progression-free survival

Average length of time from start of treatment until disease progression or death.

Recurrent or relapsed cancer

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

Refractory disease

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

Response rate

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

Standard of care

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

Systemic therapy

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

Results of a recent clinical study among patients with early-stage cervical cancer who underwent either a radical hysterectomy or a simple hysterectomy showed that rates of cancer recurrence were low (less than 3 percent), regardless of the procedure the participant received (528). However, those who had a simple hysterectomy experienced fewer side effects, such as urinary incontinence and urinary retention, and a better quality of life, supporting the use of the less extensive procedure.

While less invasive approaches to surgery are promising, it is vital that their benefits, as well as any adverse effects on long-term patient survival, are tested in rigorous, well-designed, larger and diverse clinical trials before they can become standard of care.

Visualizing Breast Cancer Cells More Precisely During Surgery

Breast cancer is the most common cancer and the second leading cause of cancer death in women in the United States. Many patients with breast cancer are treated with lumpectomy,

also called breast-conserving surgery, a procedure performed to remove cancerous tissue and some normal tissue around it, but not the breast itself. Residual tumor cells left behind after surgery may pose a risk for breast cancer recurrence. Currently, surgeons use pathologic tests that identify tumor cells at or near the lumpectomy-derived tissue margin to determine residual tumor. However, these approaches are flawed, since a proportion of patients do experience local recurrence necessitating a second surgery.

In April 2024, FDA approved the imaging molecule pegulicianine (Lumisight) and the Lumicell Direct Visualization System for adult patients with breast cancer undergoing lumpectomy to help detect residual cancerous tissue within the breast following removal of the main tumor. Pegulicianine is injected into the patients 2 to 6 hours prior to surgery. The molecule reacts with enzymes that are found at high levels in and around tumor cells, which leads to a fluorescent signal that can be detected by a handheld probe and a tumor detection algorithm (Lumicell). The surgeon can thereby identify suspicious areas in the breast where residual cancer may remain after the main resection and perform a targeted removal of the suspicious tissue to avoid future surgeries.

The approval was based on findings of a clinical trial which showed that the imaging system helped detect and remove tumors left behind after standard lumpectomy in nearly 8 percent (27 out of 357) of patients who received the agent. In 19 of these 27 patients, standard pathology evaluation did not find any cancers, and the residual cancer would have been missed without Lumisight (530). Further research is needed to overcome current limitations of this technology, including low sensitivity—not all patients who receive a negative result are free of residual cancer—as well as severe life-threatening allergic reactions in certain patients.

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. 85). Radiotherapy plays a central role in the management of cancer and works primarily by damaging DNA, leading to cancer cell death.

There are many types and uses of radiotherapy (see **Sidebar 29**, p. 92). 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 (531). Because of the central role of radiotherapy in the treatment and management of cancer, researchers are continually innovating radiotherapeutic approaches to maximize the benefit for patients, while minimizing potential harms associated with the use of radiation (see **A New Age of Radiation Therapy**, p. 150).

Despite the immense benefits of radiotherapy, the long-term effects can negatively impact a patient's quality of life. Researchers are evaluating approaches to make radiotherapy safer and more effective and identify when radiotherapy can be reduced or even avoided without affecting the outcomes for patients. As one example, several recent studies have shown that patients with very low-risk early-stage breast cancer with certain molecular characteristics who received lumpectomy can forgo radiation therapy without any excess risk of cancer recurrence, as long as they receive guideline-adherent treatment with hormone therapies (532-534).

Stereotactic body radiotherapy (SBRT) is an advanced approach to radiotherapy that can target radiation to tumors more precisely than traditional radiotherapy. Greater precision of the procedure means that higher doses of radiation can be used compared with traditional radiotherapy and that healthy tissues surrounding a tumor are spared from damage caused by the radiation, which can reduce the long-term adverse effects of radiotherapy. Given the potential benefits of SBRT, there are many clinical trials testing ways to incorporate these treatments into clinical cancer care. As one example, for certain patients with localized kidney cancer for whom surgery is not an option, SBRT was shown to be highly effective in keeping their cancers at bay and improving survival (535). This finding provides new hope to patients, especially those with large kidney tumors for whom surgery is not a viable option because of comorbidities such as obesity, cardiovascular disease, or chronic kidney disease.

ACCORDING TO THE NATIONAL CANCER INSTITUTE:

oligometastasis
(AH-lih-goh-meh-TAS-tuh-sis)
noun
A type of metastasis in which cancer cells from the original body site form a small number of new tumors in one or two other parts of the body.

oligoprogression
(AH-lih-goh-pruh-GRESH-uhn)
noun
Disease progression at a limited number of sites (up to 5).

W32

SIDEBAR 29

Using Radiation in Cancer Treatment

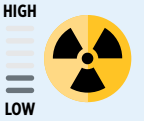
There are two major applications of ionizing radiation in cancer care:

Treatment of cancer

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

Detection of cancer

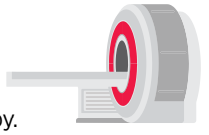
Radiology largely uses low-energy radiation to image tissues to diagnose the disease.



Types of Radiotherapy

EXTERNAL BEAM RADIOTHERAPY

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



There are several types of external beam radiotherapy:

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

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 and are said to have oligometastatic disease (536). Additionally, studies have shown that stereotactic radiotherapy targeted to oligometastatic or oligoprogressive tumors can reduce the chances of disease progression and increase survival for patients who have solid tumors, such as prostate cancer, lung cancer, or gynecologic cancers (537-539). For example, according to findings from a new clinical trial, adding SBRT targeted at oligoprogressive sites to standard treatment for patients with lung cancer led to more than a four-fold increase in progression-free survival compared to standard treatment (540).

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 (541). Thus, patients who have hypofractionated radiotherapy complete their radiotherapy over a shorter period and in fewer treatment sessions. Researchers are also testing whether lowering the dose of radiotherapy, which may spare patients from many of the adverse effects of treatment, can still manage cancer effectively. As one example, a recent study suggests that an individualized radiation therapy regimen, including doses lower than those routinely administered for patients with non–small cell lung cancer (NSCLC), can still prevent tumor recurrence (542).

One of the most exciting new areas in radiation oncology is the use of molecularly targeted radiotherapeutics—radiation-emitting molecules that are linked to targeting molecules which steer the radiation specifically to cancer cells (see **Emergence of Radiotheranostics**, p. 151). Several such therapeutics have been approved by FDA in recent years for the treatment of a variety of cancer types (1,73,543), and several more are at various stage of clinical testing (see **Table 8**, p. 152). As one example, in January 2018, Lu-177 dotatate was approved for treating patients with gastroenteropancreatic neuroendocrine tumors whose cancer had progressed after prior treatments (543).

Research has shown that most neuroendocrine tumors have the protein somatostatin receptor on their cell surface. In Lu-177 dotatate, the radionuclide Lu-177 is linked to a molecule that is analogous to somatostatin which targets the radiation to somatostatin receptor–positive cancer cells. More recently, a clinical study showed that Lu-177 dotatate can be a promising option even as the initial therapy for certain patients with neuroendocrine tumors (544). In the trial, patients who received Lu-177 dotatate lived nearly three times as long without their cancer getting worse, compared to the control group. These findings bring hope to many more patients with this rare but aggressive cancer.

Advances in Treatment With Cytotoxic Chemotherapy

Cytotoxic chemotherapy—use of chemicals to kill cancer cells—was first introduced as a pillar of cancer treatment in the early to mid-20th century (506). Chemotherapy remains a backbone of cancer treatment and its use is continually evolving to minimize potential harm to patients, while maximizing its benefits.

As with surgery and radiotherapy, chemotherapy is more commonly used to treat cancer in combination with one or more additional types of treatments. Newer and more effective chemotherapeutics continue to be evaluated in clinical research. In addition, FDA routinely expands the use of previously approved chemotherapeutics for additional cancer types through review of new clinical trials, as well as by monitoring of current real-world use of such agents. The FDA Project Renewal leverages expertise of clinical researchers to review existing published literature on drug utilization and maintain updated labeling of older, commonly prescribed anticancer therapeutics. For instance, in September 2023, FDA approved updated labeling for the chemotherapeutic temozolomide (Temodar), which included new indications and dosing regimen.

Treatment with cytotoxic 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. Researchers are investigating different approaches to make chemotherapeutics safer for patients. Areas of ongoing investigation include designing modifiable chemotherapeutics, e.g., with "on" and "off" switches, that are selectively delivered to tumors while sparing healthy tissue; evaluating less aggressive chemotherapy regimens that can allow patients the chance of an improved quality of life without compromising survival; identifying patients for whom chemotherapy has no added benefit; and identifying biomarkers such as circulating tumor DNA to correctly predict which patients will or will not benefit from chemotherapy.

As one example, data from a recent retrospective analysis showed that patients with a certain subtype of breast cancer, known as estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative invasive lobular carcinoma, who are treated with hormone therapy do not derive any additional benefit from chemotherapy (545). Data from a separate clinical trial showed that circulating tumor DNA can be a promising way to identify patients with colorectal cancer who can safely forgo postsurgical chemotherapy without a risk of cancer recurrence (546).

Another recent development in cancer chemotherapy was FDA approval of the chemotherapeutic melphalan as the first liver-directed treatment for uveal melanoma that has metastasized to

SIDEBAR 30

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, e.g., bevacizumab (Avastin).

Cell-lysis mediators

Cause cancer cell death via different mechanisms, e.g., 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, e.g., receptor tyrosine kinase inhibitors, such as the epidermal growth factor receptor (EGFR)–targeted therapeutic osimertinib (Tagrisso).

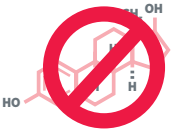
DNA-repair inhibitors

Prevent cancer cells from repairing their damaged DNA, causing them to die, e.g., poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib (Lynparza).

Epigenome-modifying agents

Block proteins that epigenetically modify DNA, e.g., panobinostat (Farydak).

Hormones/Antihormones



Block hormones such as estrogen or testosterone that drive cancer development, e.g., 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, e.g., bortezomib (Velcade).

Radiation-emitting therapeutics/ Radioconjugates

Deliver high doses of radiation to cancer cells, leading to cancer cell death, e.g., lutetium Lu-177 dotatate (Lutathera).

These therapeutics have revolutionized cancer treatment in recent decades and the greater precision of these molecularly targeted treatments tends to make them more effective and less toxic than chemotherapeutics.

the liver. Uveal melanoma is a rare cancer that develops in the eye and has a high tendency to metastasize. Liver metastases occur in up to 95 percent of patients with metastatic disease, and these lesions are often inoperable. The newly approved Hepzato kit includes melphalan and a device through which the chemotherapeutic is infused into the hepatic artery. This administration method allows for delivery of a higher dose of chemotherapy directly to the liver while avoiding toxicity to other tissues.

Advances in Treatment With Molecularly Targeted Therapeutics

Remarkable advances in our understanding of the biology of cancer, including the identification of numerous genetic mutations that fuel tumor growth, have set the stage for a new era of precision medicine, an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the individual patient and the characteristics of that patient's cancer dictates the best treatment option for the patient (see **Understanding the Path to Cancer Development**, p. 26).

Therapeutics directed to molecules influencing cancer cell multiplication and survival target tumor cells more precisely than cytotoxic chemotherapeutics, which generally target all rapidly dividing cells, and thereby limit damage to healthy tissues. The greater precision of these molecularly targeted therapeutics tends to make them more effective and less toxic than cytotoxic chemotherapeutics (see **Sidebar 30**, p. 94). As a result, they are not only saving lives but also

allowing patients with cancer to have a higher quality of life. 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 molecularly targeted treatments among patients from racial and ethnic minorities and other medically underserved populations (29,497). It is vital that ongoing research and future public health policies are aimed to ensure equitable access to precision cancer medicine, including tumor genetic testing and the receipt of molecularly targeted therapeutics for all patients.

In the 12 months spanning July 1, 2023, to June 30, 2024, FDA approved eight new molecularly targeted anticancer therapeutics (see **Table 7**, p. 86). During this period, FDA also expanded the use of 11 previously approved molecularly targeted anticancer therapeutics for treating additional types of cancer.

Expanding Precision Treatments Against Common Cancer Types

Common cancer types are those that are diagnosed with the highest frequency in the United States. Cancers of the breast, colon and rectum, lung, and prostate are the most common cancers diagnosed, with an estimated 313,510, 152,810, 234,580, and 299,010 new cases, respectively, expected in the United States in 2024 (3). Together, these cancers will be attributable to more than 40 percent of all cancer deaths in the United States in 2024. While researchers are continually evaluating new and improved treatments for these cancers and mortality from these diseases has been declining steadily, additional research and innovation are urgently needed considering the ongoing burden of these four cancers, especially in selected population groups, e.g., colorectal cancer in people younger than 50 and lung cancers among women without a history of smoking. FDA decisions made during the 12 months covered in the report are providing new and expanded therapeutic options for patients with breast, colorectal, lung, and prostate cancers.

Despite major advances in the treatment of breast cancer, this disease is the second leading cause of cancer-related death for women in the United States (2). A recent FDA decision has the potential to further accelerate progress against breast cancer because it has provided a new molecularly targeted treatment option for certain patients with the disease.

For patients with breast cancer, one factor determining what treatment options should be considered is the presence or absence of three tumor biomarkers, two hormone receptor (HR) proteins and the HER2 protein. About 70 percent of breast cancers diagnosed in the United States are characterized as HR-positive and HER2-negative (547). Potential treatment options for these patients include an antihormone therapeutic, such as tamoxifen, which works by preventing the hormone estrogen from attaching to its receptor; or letrozole, which works by lowering the level of estrogen in the body; or fulvestrant, which works by destroying estrogen receptors (ER), alongside a cyclin-dependent kinase 4/6 inhibitor. Treatment with anti-hormone therapeutics is also called endocrine therapy.

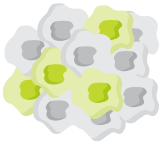
Unfortunately, most advanced, HR-positive breast cancers that initially respond to endocrine therapy eventually progress because they have become treatment resistant (see **Sidebar 31**, p. 95). Research has shown that a signaling

SIDEBAR 31

The Challenge of Treatment Resistance

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

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

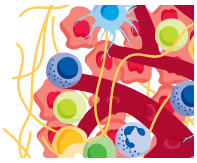


Some cancer cells in a tumor may have or **may acquire mutations** in the target of a given treatment that render the treatment ineffective in those cells and their progeny.

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

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

Differences in tumor microenvironment components can render a treatment ineffective.



Source: (550).

USE OF PI3K INHIBITOR IN BREAST CANCER PATIENTS **VARIES BY SOCIOECONOMIC FACTORS,** WITH LOWER LIKELIHOOD OF USE **AMONG PATIENTS ON MEDICAID COMPARED TO THOSE WITH PRIVATE INSURANCE AND** HIGHER USE AMONG PATIENTS TREATED AT AN ACADEMIC CENTER.

Source: (549).

W33

pathway that is vital for driving cell multiplication and survival, and involves PI3K, AKT, and PTEN proteins, is overactivated in approximately half of HR-positive, HER2-negative breast cancers through activating mutations in PI3K or AKT and/or inactivating mutations in PTEN (548). Overactivation of PI3K–AKT–PTEN signaling has been implicated in the development of endocrine therapy resistance. A molecularly targeted therapeutic, alpelisib (Piqray), which blocks the function of PI3K, was approved for patients with breast cancer in 2019.

The protein AKT, also known as protein kinase B, plays a central role in PI3K–AKT–PTEN signaling. In November 2023, FDA approved capivasertib (Truqap), the first molecularly targeted therapeutic that acts by blocking the function of AKT. Together with alpelisib, capivasertib is now the second molecularly targeted therapeutic against the PI3K–AKT–PTEN pathway and is benefiting patients with invasive lobular breast cancer such as **Julia K. Levine** (see p. 99).

Capivasertib was approved for use in combination with fulvestrant for adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more alterations in *PI3K*, *AKT*, or *PTEN* genes, as detected by an FDA-approved test, following progression on or after endocrine therapy. At the same time, FDA also approved the FoundationOne CDx assay as a companion diagnostic test (see **Sidebar 32**, p. 96) to identify patients with breast cancer who are eligible for treatment with capivasertib. FDA approval was based on results from a phase III clinical trial showing that patients who received capivasertib along with fulvestrant had a 40 percent reduction in the risk of disease progression or death compared to patients who received fulvestrant alone and that adding capivasertib to fulvestrant almost doubled the time before disease progression (548).

Colorectal cancer is the fourth most common cancer and the second most common cause of cancer mortality in the United States. Notably, over the past few decades, there has been an increase in the incidence of early-onset (those cases diagnosed in patients younger than 50 years) colorectal cancer. Additionally, the incidence and mortality are higher in certain racial and ethnic minority groups, such as American Indian or Alaska Native and Non-Hispanic Black populations (3).

SIDEBAR 32

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.

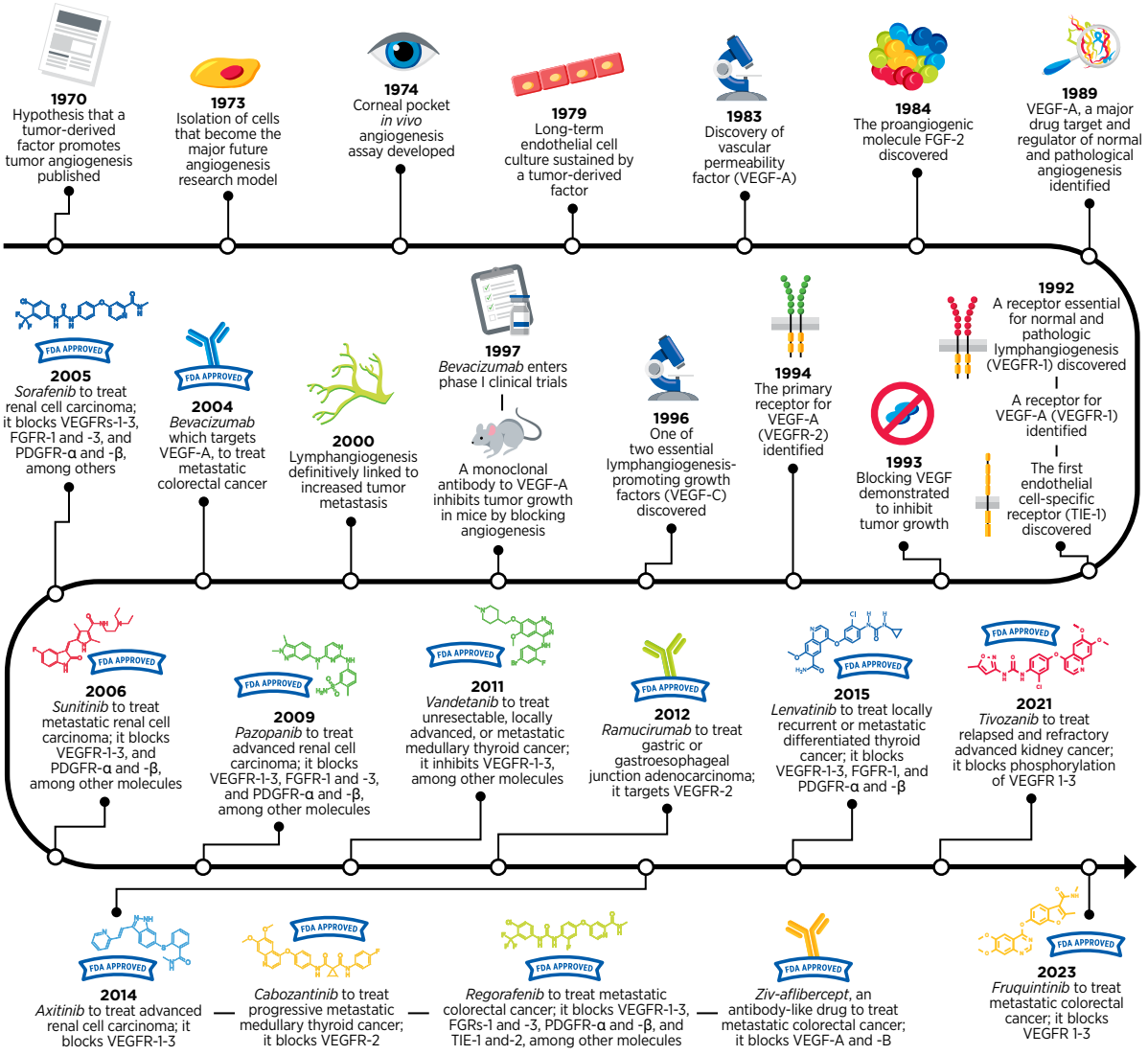
Source: (551).

Solid tumors such as colorectal cancers can be highly dependent on the growth of new blood and lymphatic vessels, a phenomenon referred to as angiogenesis, to grow and survive (see **Systems That Enable Cancer Progression**, p. 34). Thus, targeting these key components of the tumor microenvironment (see **Sidebar 8, p.** 38) provides an ideal avenue for therapeutic intervention. In fact, researchers have developed many molecules, called antiangiogenic drugs or angiogenesis inhibitors, that work in similar ways to impede the growth of the new blood and lymphatic vessel networks that enable cancer cells to thrive, and as of June 30, 2024, FDA has approved 13 such therapeutics (see **Figure 17**, p. 97).

Antiangiogenic drugs mainly function by stopping members of a family of growth-promoting proteins called VEGFs from activating the molecules they attach to, VEGF receptors, which are abundant on the cells that make up blood and lymphatic vessel walls and are vital for blood vessel formation. Antiangiogenic therapeutics have had the biggest impact for adult patients with the most common type of kidney cancer,

FIGURE 17

Targeting Tumor's Blood Supply



Since the hypothesis more than 50 years ago that tumors secrete a factor that enhances formation of new blood vessels (angiogenesis) in and around the tumor tissue, breakthrough discoveries have fueled the development of molecularly targeted therapeutics that inhibit tumor angiogenesis and result in tumor shrinkage and/ or elimination. Over the past two decades, the US Food and Drug Administration (FDA) has approved 13 such anticancer therapeutics, also called antiangiogenic agents. Bevacizumab (Avastin) was the first of these drugs to be approved, in 2004, and fruquintinib (Fruzaqla) was the most recent, in 2023. Research into angiogenesis under both normal and pathologic conditions, including cancer, helped identify many of the molecular regulators of these processes, and these regulators are the specific targets of the antiangiogenic agents. The year when each of these therapeutics was first approved is indicated on the timeline; however, most agents received approval from FDA for the treatment of additional cancers in subsequent years.

continued on page 100

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

Julia K. Levine

Venice, California

In January 2013, Julia K. Levine, a 25-year veteran in the film and television industry, noticed what looked like bruises on her left breast. Her doctor recommended a mammogram, which found a suspicious area. After additional tests, Julia was diagnosed with metastatic lobular breast cancer. Julia had no family history of cancer, so it came as a shock that she had a 7-centimeter tumor in her breast, and that the cancer had spread to her bones.

For the first 5 years of her ongoing treatment, Julia felt good and was able to continue working. But as her treatments and the side effects became more difficult, she had to step away from her demanding career. "Cancer diagnosis was affecting everything in my life, including career and finances," Julia recalled. And while she was close with her son, who was in high school at the time of her diagnosis, she also had to make a tough decision about how much he should know. "He was old enough to know about breast cancer. But I wanted him to maintain a normal life, so I was careful about how much detail to share."

"Do as much evidence-based research as possible, go to conferences, meet other advocates, and don't be afraid to talk to scientists. Most importantly, advocate for yourself."

Julia's first treatment was with an antiestrogen drug, anastrozole, to shrink the tumor, followed by surgery to remove it. But, as she later learned, lobular breast cancer does not have distinct lumps, making it difficult to surgically remove with clear margins. Over the next 6 years, Julia underwent two more surgeries, followed by radiation therapy in 2019. Around the same time, she started taking a new therapeutic, palbociclib with fulvestrant. Unfortunately, after about a year the cancer that had metastasized to her bones started to progress. At that point, she began an oral chemotherapeutic, capecitabine, which controlled her disease for 2½ years.

In 2022, Julia participated in a phase Ib clinical trial at UCLA for an investigational drug. Even though it did not work for her, the treatment worked for others, so Julia was happy to contribute to science in some way. Julia knows it is important to participate in clinical trials. It was even more meaningful for her because there are not many clinical trials for patients with lobular breast cancer and bone-only metastatic disease as they do not often qualify for clinical trials.

"I am grateful for the people who came before me. This is the way new drugs get approved, and we need new drugs to stay alive. We need to be more inclusive and diverse in age, race, ethnicity, and in subtypes of cancer, because everybody's different," Julia emphasized.

For the past 5 months, Julia has been taking capivasertib, which was approved by the US Food and Drug Administration in November 2023. Julia had been anxiously awaiting that approval because her previous treatment, everolimus, came with significant side effects. Even though she has experienced some challenging gastrointestinal side effects and has lowered the dose with capivasertib and has rising levels of some tumor markers, her scans are showing reduction of her bone and bone marrow metastases.

"I'm feeling pretty good. I have more energy than I've had in the past year. I do physical therapy and yoga, and I like walking on the beach. I'm designing a new back porch. I do some artwork, and I read all the time. I play tambourine in my husband's band, which is fun. I love to dance, and I like to work in my garden," Julia said.

Julia loves doing research. She did it previously for her job, and following her cancer diagnosis, she researched metastatic lobular breast cancer, attended scientific conferences, met with scientists and researchers, and bonded with patients and patient advocates. Her passion to stay informed about the progress being made against the disease led Julia and some scientists and other patient advocates to found the Lobular Breast Cancer Alliance in 2016; LBCA has become a go-to resource for patients with lobular breast cancer.

"It's so important for people with a disease that's not well known to find accurate information about it, meet other people who have the same diagnosis, and/or are on the same drugs you are on. It's lonely when you have a disease and you don't know anybody else who has that disease," Julia said.

When she was initially diagnosed with metastatic cancer, Julia wasn't sure she would see significant milestones. Now she will celebrate her 30th wedding anniversary with a trip to Europe. And she is grateful to witness her son, now 26, graduate college, get a good job, and have a long-time girlfriend. Julia has also become a fierce advocate for more funding for cancer research and for allowing patients with metastatic lobular breast cancer to enroll in clinical trials. She is a co-author on academic publications, routinely participates in scientific conferences as a speaker, and is helping promote the first Lobular Breast Cancer Awareness Day on October 15, 2024.

"I can't stress enough the importance of funding for metastatic cancer. For example, metastatic breast cancer only garners about 13 percent of all breast cancer research, and lobular breast cancer is only about 1 percent. Research and clinical trials save lives and metastatic cancer kills, so we need to do more," Julia emphasized. And for people interested in patient advocacy, Julia's advice is apt: "Do as much evidence-based research as possible, go to conferences, meet other advocates, and don't be afraid to talk to scientists. Most importantly, advocate for yourself."

renal cell carcinoma. However, they also greatly benefit patients with the most aggressive form of liver cancer, as well as those with some forms of pancreatic cancer; some gastrointestinal stromal tumors and soft-tissue sarcomas; and some thyroid, lung, and colorectal cancers.

A new therapeutic option in this growing class of drugs is fruquintinib (Fruzaqla), which was approved by FDA in November 2023 for the treatment of patients with metastatic colorectal cancer who received prior treatments with chemotherapy, an anti-VEGF therapeutic, and for certain patients an EGFR-targeted therapy. The approval was based on findings from two phase III clinical trials, both of which showed superior survival among patients treated with fruquintinib compared to their respective control groups (552,553). This new treatment is taken orally and offers a survival benefit for patients who have received multiple prior therapies and may be out of options, thereby fulfilling a critical unmet need in metastatic colorectal cancer.

Nearly 80 percent of lung cancers diagnosed in the United States are classified as non–small cell lung cancers (NSCLC). In the past decade, researchers have significantly increased our understanding of the genetic changes that fuel NSCLC growth, which has led to the development of therapeutics that target many of these changes (see **Figure 1**, p. 13). 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 (554), molecular testing rates and targeted therapy use remain low and there are wide variations across health care practices (555). Broad implementation of cutting-edge molecular testing to simultaneously identify all genetic alterations driving NSCLC that could be therapeutically targeted offers meaningful benefits to patients and is estimated to be cost-effective (556).

About 2 percent of NSCLC cases are fueled by genetic alterations known as chromosomal translocations that involve the *ROS1* gene and lead to the production of ROS1 fusion proteins (557). The ROS1-targeted therapeutic repotrectinib (Augtyro) was approved by FDA in November 2023 for patients with advanced or metastatic NSCLC with ROS1 fusions as an initial treatment or as the second treatment in those who previously received another ROS1-targeted drug. FDA approval was based on findings from a clinical trial that showed tumor shrinkage in nearly 80 percent of the study participants who had not previously received a ROS1-targeted drug, and in nearly 40 percent of participants who had already received another ROS1-targeted drug, such as crizotinib (Xalkori) or entrectinib (Rozlytrek) (557). The median time before the disease worsened was nearly 36 months among participants who had not previously received a ROS1-targeted drug and 9 months among those who had previously received a ROS1-targeted drug.

Notably, repotrectinib was able to shrink tumors that had spread to the brain, a common location for lung metastases. Another advantage of treatment with repotrectinib is that it is effective against tumors expressing certain mutated forms of ROS1, including one called G2032R, that render other ROS1-targeted drugs, crizotinib and entrectinib, ineffective. In the clinical trial, nearly 60 percent of patients whose tumors had the G2032R mutation responded to repotrectinib.

In addition to ROS1 fusion protein, repotrectinib also targets three other related proteins called TRKA, TRKB, and TRKC. The genes *NTRK1*, *NTRK2*, and *NTRK3* provide the code that cells use to make these proteins. Research has shown that chromosomal translocations that involve the three *NTRK* genes and lead to the production of TRK fusion proteins drive the growth of up to 1 percent of all solid tumors. A significant advance in precision medicine during the 12 months spanning this report was the FDA approval of repotrectinib to treat adult and pediatric patients aged 12 years or older (see **Research-driven Progress Against Childhood and AYA Cancers**, p. 115) who have solid tumors that test positive for the *NTRK* gene fusions.

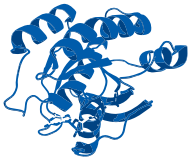
Although in this section we focus on the approval of new anticancer therapeutics, it should be noted that several previously approved molecularly targeted therapeutics received expanded approval by FDA for the treatment of additional cancer types in the 12 months covered by the report. As one example, in August 2023, FDA approved the molecularly targeted therapeutic niraparib (Zejula) in combination with the antihormone therapy abiraterone acetate (Zytiga), for certain adult patients with metastatic prostate cancer that is fueled by a mutation in the *BRCA* gene, as determined by an FDA-approved test.

This was the first FDA approval of niraparib for the treatment of prostate cancer. However, it was previously approved for treatment of certain patients with cancers of the ovary, fallopian tube, and peritoneum. Along with olaparib (Lynparza) and rucaparib (Rubraca), two additional molecularly targeted therapeutics that work in the same way and have already been approved by FDA, the recent approval of niraparib expands available treatment options for metastatic prostate cancer harboring a mutation in the *BRCA* gene.

Another significant expansion of a previously approved therapeutic that occurred in the 12 months covered in this report was the June 2024 FDA approval of the KRAS-targeted therapeutic adagrasib (Krazati) in combination with cetuximab (Erbitux) for adults with locally advanced or metastatic colorectal cancer that has a mutation known as

SIDEBAR 33

Targeting the Undruggable KRAS



Mutated *KRAS* represents one of the most common genetic alterations in human cancers. Nearly 50 percent of patients with colorectal cancer have mutations in *KRAS*. The G12C mutation occurs in 3 to 4 percent of patients with colorectal cancer and causes the KRAS protein to prefer an "on" or "active" state, leading to uncontrollable cell growth that can form tumors (558). Historically, KRAS has been considered an undruggable target because of the difficulties in designing a therapeutic that could selectively bind and inhibit KRAS. Thanks to enhanced understanding of KRAS biology and unprecedented progress in structural biology and drug design, the US Food and Drug Administration (FDA) has recently made the following decisions:

2021

Sotorasib (Lumakras) became the first ever KRAS-targeted therapeutic approved for patients with non–small cell lung cancer (NSCLC).

2022

A second KRAS-targeted therapeutic, **adagrasib (Krazati), was approved**, also for the treatment of NSCLC.

2024*†

Approval of adagrasib was expanded, in combination with cetuximab, another molecularly targeted therapeutic which blocks the function of a protein known as EGFR, **for certain patients with colorectal cancer**.

* Research shows that in patients with colorectal cancer that have KRAS G12C mutations dual targeting of both KRAS and EGFR pathways is more effective than inactivation of KRAS alone. This is because blocking KRAS alone may lead to an adaptive response in cancer cells leading to reactivation of the RAS pathway mediated by EGFR (559).

† FDA approval was based on results from a phase I/II clinical trial in which the tumors shrank in 34 percent of patients receiving adagrasib with a median duration of response of nearly 6 months (560).

KRAS G12C, as determined by an FDA-approved test (see **Sidebar 33**, p. 101). Adagrasib was previously approved for certain patients with NSCLC and ongoing research is evaluating its efficacy in patients with pancreatic cancer, such as **Dr. Humberto M. Guiot** (see p. 103).

Personalizing Treatment for Patients With a Rare Solid Tumor

Rare cancer is defined by the National Cancer Institute (NCI) as cancer that occurs in fewer than 15 out of 100,000 people each year. Rare cancers can be challenging for researchers to study and for physicians to treat (see **Sidebar 34**, p. 104). During the 12 months covered by this report (July 1, 2023, to June 3, 2024), FDA approved molecularly targeted therapeutics and immunotherapeutics for treating a number of rare cancers, bringing the promise of precision medicine to patients who often have few treatment options.

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 childhood, teen, and young adults faster.

Desmoid tumors are an extremely rare and potentially debilitating condition that affects an estimated 1,650 people in the United States each year. Also known as aggressive fibromatosis, desmoid tumors mainly affect young individuals but can also develop in people of any age. Those with the inherited condition familial adenomatous polyposis are at a particularly high risk (see **Table 4**, p. 71) (561). While desmoid tumors do not have the ability to metastasize, they grow fast and can invade locally, causing debilitating pain and deformity and, in extreme cases, life-threatening organ damage.

Currently, there is no standard treatment for desmoid tumors. Surgery and chemotherapy are the most common interventions, but the disease comes back often after treatment. Therefore, the first-ever FDA approval of a therapeutic for adults with desmoid tumors, nirogacestat (Ogsiveo), in November 2023 is a major breakthrough for these patients. Nirogacestat blocks the activity of an enzyme called gamma secretase, which is involved in driving desmoid tumor growth through the activation of a signaling protein called Notch. Researchers have hypothesized that desmoid tumors produce high amounts of Notch protein, which is thought to drive their growth.

FDA approval was based on results of a phase III clinical trial in which 41 percent of patients treated with nirogacestat had tumor shrinkage, compared to only 8 percent of those in the control group (562). Among patients who had tumor shrinkage with nirogacestat, tumors completely disappeared in 7 percent of people, compared to none in the control group. After 2 years of treatment, there was no evidence of tumors getting worse in 75 percent of patients who received nirogacestat, compared to just 44 percent of patients in the control group.

continued on page 104

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

Dr. Humberto M. Guiot

Guaynabo, Puerto Rico

Dr. Humberto M. Guiot, a distinguished 46-year-old infectious disease physician and professor of medicine at the University of Puerto Rico, was at the pinnacle of his career. With roles as an educator, clinical researcher, President of the Infectious Diseases Society of Puerto Rico, and Dean of the School of Medicine, as well as an active clinical practitioner, his work life was full. In addition, he and his husband were moving Humberto's mother, who was being treated for breast cancer, in with them. Then, in the winter of 2022, everything changed.

"My life is an example of how much clinical trials can help patients. A few months ago, I thought that everything was over. And if it were not because of clinical trials, I would not be here right now."

It began with a persistent pain in his flank and back that gnawed at him through the holidays, making sleep elusive and daily activities burdensome. As a doctor, Humberto initially assumed he was suffering from a musculoskeletal issue, perhaps the result of his demanding workload. But when the pain refused to subside and his weight began to drop, he realized it might be something more serious.

After weeks of tests and consultations, a large mass was discovered near his left kidney. The news was devastating. What initially appeared to be a kidney tumor turned out to be an adenocarcinoma of pancreatic origin—pancreatic cancer. The diagnosis in March 2023 left him reeling. As a physician, he knew the grim prognosis associated with pancreatic cancer. He understood the aggressiveness of the disease and the limited effectiveness of available treatments. "I was devastated because I knew it was a very hard road for me," Humberto said.

He had always been the one providing care, offering hope to his patients, but now, as he grappled with his own diagnosis, Humberto was overwhelmed. The cancer was advanced, involving several organs, and surgery was not initially an option. He wanted a second opinion and traveled to a cancer center in New York. He was advised to start with conventional chemotherapy, locally in Puerto Rico, with the hope that the tumor would shrink enough to make surgery a viable option.

Chemotherapy was grueling. The side effects were severe: weight loss, hair loss, bleeding, anemia, superimposed infections, and relentless fatigue. Humberto found himself in and out of the hospital, struggling with complications and the emotional toll of his condition. "I was very weak. I required admission to the hospital several times for transfusions or because of fever and for different complications," he said. However, amid all the adversities and suffering, there was a glimmer of hope—the tumor was shrinking.

By July 2023, the tumor had reduced in size, and surgery was finally an option. Humberto traveled back to New York for the surgery. The operation was extensive, requiring the removal of several organs. The recovery was difficult. "But I was happy that I was recovering well. In the back of my mind, I knew that I had to go back to chemo, which was very hard the first time. I didn't know what to expect after having several organs removed and after losing so much weight."

In August 2023, Humberto was back in Puerto Rico to complete the courses of chemotherapy. However, as the year drew to a close, his treatment became more difficult. By December 2023, Humberto was practically bedridden, losing more weight, and barely able to perform basic tasks. The holidays were a blur of pain and exhaustion. Then, in early January 2024, he received more grim news: The cancer had progressed, spreading to distant organs.

A ray of hope emerged through genetic testing, which revealed a mutation in the *KRAS* gene that made him eligible for a clinical trial involving a new molecularly targeted treatment, adagrasib (Krazati). Though skeptical, Humberto, bolstered by the optimism of his husband and medical team, decided to pursue this opportunity.

The first infusion was incredibly challenging, but within days, Humberto began to feel better. His symptoms improved rapidly, and by the time of his second infusion, he was able to walk unaided and even stopped taking pain medication. His lab results improved, and by April 2024, he was in complete remission—a stunning turnaround from the dire prognosis just a few months earlier.

Today, Humberto has regained much of the life he thought he had lost. He is back at work, not only as a physician but also as the interim executive director of the University of Puerto Rico Comprehensive Cancer Center. His personal battle with cancer has given him a renewed purpose, to help other patients navigate their own journeys. He is committed to ensuring that other patients have the same opportunities for recovery and quality of life that he was fortunate to experience.

Humberto's story is a testament to the power of medical research. "My life is an example of how much clinical trials can help patients to go back to their life and to serving their community. A few months ago, I thought that everything was over when conventional therapies had failed me. And if it were not because of clinical trials, I would not be here right now. Since my treatment, I have visited Europe twice, taken a cruise, and am back to work. And everything has been possible because of clinical trials."

SIDEBAR 34

The Challenges Posed by Rare Cancers

Rare cancers affect fewer than 40,000 people per year in the United States. 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.

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

Adding Precision to the Treatment of Blood Cancers

Cancers that arise in blood-forming tissues, such as the bone marrow, or in cells of the immune system, are called blood cancers, or hematologic cancers. In the 12 months covered by this report, FDA has made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers (see **Sidebar 35**, p. 105).

Acute myeloid leukemia (AML) is the most commonly diagnosed leukemia in the United States, with 20,800 new cases anticipated in 2024 (2). AML has only 32 percent overall 5-year relative survival rate, the lowest among leukemias (3). Research has substantially increased our understanding of the biology of AML, in particular the different types of genetic mutations that promote AML development. This knowledge is fueling the emergence of molecularly targeted therapeutics for defined groups of patients with the disease.

Mutations in the *FLT3* gene promote the multiplication and survival of AML cells in 25 to 30 percent of cases, and patients with this type of AML have particularly poor outcomes (563). In July 2023, FDA approved a new molecularly targeted

SIDEBAR 35

Recent Advances Against Blood Cancers

Between July 1, 2023, and June 30, 2024, the US Food and Drug Administration made several decisions that are providing new treatment options to patients with blood cancers. Among the newly approved therapeutics and expansions of previously approved therapeutics for a new blood cancer type are the following:

Approved in 2023

JULY

Acute Myeloid Leukemia

Quizartinib (Vanflyta), a molecularly targeted therapeutic.

AUGUST

Multiple Myeloma

Elranatamab-bcmm (Elrexfio), a T cell-engaging bispecific antibody (a type of immunotherapeutic).

Talquetamab-tgvs (Talvey), a T cell-engaging bispecific antibody (a type of immunotherapeutic).

SEPTEMBER

Myelofibrosis

Momelotinib (Ojjaara), a molecularly targeted therapeutic.

OCTOBER

Myelodysplastic Syndrome

Ivosidenib (Tibsovo), a molecularly targeted therapeutic.

DECEMBER

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Pirtobrutinib (Jaypirca), a molecularly targeted therapeutic.

Approved in 2024

MARCH

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Lisocabtagene maraleucel (Breyanzi), a CAR T-cell therapy (a type of immunotherapeutic).

Follicular Lymphoma

Zanubrutinib (Brukinsa), a molecularly targeted therapeutic.

MAY

Follicular Lymphoma

Lisocabtagene maraleucel (Breyanzi), a CAR T-cell therapy (a type of immunotherapeutic).

Mantle Cell Lymphoma

Lisocabtagene maraleucel (Breyanzi), a CAR T-cell therapy (a type of immunotherapeutic).

JUNE

Follicular Lymphoma

Epcoritamab-bysp (Epkinly), a T cell-engaging bispecific antibody (a type of immunotherapeutic).

Myelodysplastic Syndrome

Imetelstat (Rytelo), a molecularly targeted therapeutic.

therapeutic, quizartinib (Vanflyta), for treating adults who have newly diagnosed AML that tests positive for a mutation in the *FLT3* gene known as *FLT3* internal tandem duplication (ITD). The approval was based on results from a phase III clinical trial showing that patients who received quizartinib along with standard chemotherapy lived more than twice as long as those who received standard treatment alone (564). Quizartinib can cause several cardiac side effects and is therefore available only through a restricted program.

At the same time that FDA made the decision about quizartinib, it expanded the use of the LeukoStrat CDx *FLT3* Mutation Assay as a companion diagnostic to identify patients with *FLT3* ITD mutation–positive AML who are eligible for treatment with the new molecularly targeted therapeutic. Quizartinib is the third FLT3-targeted drug approved for the treatment of patients with AML and, along with midostaurin (Rydapt) and gilteritinib (Xospata) previously approved by FDA, expands treatment options for the subset of AML patients with the FLT3 alteration.

Myelodysplastic syndromes (MDS) are defined by the National Cancer Institute (NCI) as a diverse group of cancers in which immature blood cells in the bone marrow do not mature or become healthy blood cells. A third of patients diagnosed with

In 2009, the **Nobel Prize in Physiology or Medicine** was awarded jointly to Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak for their discovery of how chromosomes are protected by telomeres and the enzyme telomerase.

W34

MDS may progress to AML. Healthy bone marrow produces immature blood cells called stem cells, which develop into three types of mature blood cells: red blood cells, white blood cells, and platelets. In the case of MDS, the stem cells may not mature, or have a shorter life span, resulting in fewer than normal mature blood cells in the circulation.

Patients with MDS who have symptoms such as anemia, caused by their low blood cell counts, may receive curative treatments, including chemotherapy followed by stem cell transplant, or supportive care using molecularly targeted therapeutics and immune modulating agents as well as blood transfusion and erythropoiesis-stimulating agents to improve their quality of life. Unfortunately, MDS patients frequently become dependent on red blood cell transfusions, which can be associated with long-term adverse health consequences. There is an urgent need to develop better treatments that can provide patients with long-term independence from continuously receiving red blood cell transfusions.

Telomeres are protective caps at the end of chromosomal DNA that prevent damage to the inner protein-coding sequences of DNA. Telomeres naturally shorten each time a cell divides and eventually become too short to protect the DNA. This signals a normal cell to stop multiplying or to initiate cell death, thereby preventing unregulated multiplication that is a characteristic of cancer. Most cancer cells, including abnormal bone marrow cells in low-risk MDS, express telomerase, a protein that restores telomere length. By maintaining telomere length, cancer cells avoid telomere shortening and circumvent limitations to DNA replication. This allows cancer cells to multiply indefinitely.

In June 2024, FDA approved imetelstat (Rytelo) for the treatment of adult patients with lower-risk MDS with transfusion-dependent anemia who require four or more red blood cell units over 8 weeks and for whom erythropoiesis-stimulating agents are not an option. This is the first approval of a molecularly targeted therapeutic that works by blocking telomerase.

As a telomerase inhibitor, imetelstat works by preventing telomerase from performing its telomere-restoring function, thereby killing cancerous cells in the bone marrow that cause MDS. However, research indicates that the anticancer effect of imetelstat may also be driven by a novel cell death–promoting mechanism independent of telomere shortening (565). FDA approval was based on the findings of a phase III clinical trial that showed significantly improved red blood cell transfusion independence among certain MDS patients treated with imetelstat compared to the control group (566).

Myelofibrosis is a rare type of blood cancer with an incidence rate of 1.5 cases per 100,000 people in the United States (567). In more than 50 percent of cases, myelofibrosis is driven by mutations in the *JAK2* gene. In September 2023, FDA approved a new JAK2-targeted therapeutic, momelotinib (Ojjaara), for treating certain patients who have myelofibrosis.

Myelofibrosis is one of a group of six blood cancers called chronic myeloproliferative neoplasms: chronic myelogenous leukemia, polycythemia vera, primary myelofibrosis, essential thrombocythemia, chronic neutrophilic leukemia, and chronic eosinophilic leukemia. In some cases, polycythemia vera and essential thrombocythemia progress to become myelofibrosis. In this situation, the disease is referred to as secondary myelofibrosis.

Myelofibrosis usually develops slowly. Abnormal blood cells and fibers build up inside the bone marrow, which is where blood cells are made, leading to low levels of red blood cells (anemia). This causes tiredness, weakness, and shortness of breath. In addition, to make up for the low number of blood cells, the spleen begins to make blood cells, which causes the spleen to enlarge dramatically, a condition known as splenomegaly.

The likely outcome for patients diagnosed with myelofibrosis is estimated based on several risk factors. Patients with one to four risk factors—including being aged 65 or older; having anemia; experiencing fever, night sweats, or weight loss; having high white blood cell counts; and having at least 1 percent of blood cells being cancerous—are classified as having intermediate risk disease. Patients with four or more risk factors are classified as high risk.

Momelotinib was approved for treating intermediate- or high-risk myelofibrosis, including secondary myelofibrosis in adults with anemia. The approval was based on results from a phase III clinical trial that showed that treatment with momelotinib significantly reduced spleen volume and reduced myelofibrosis-related symptoms compared to placebo (568).

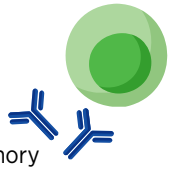
Advances in Treatment With Immunotherapeutics

The immune system is a complex network of cells (called white blood cells; see **Sidebar 36**, p. 107), tissues (e.g., bone

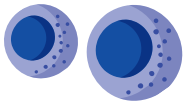
SIDEBAR 36

Key Cells of the Immune System

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



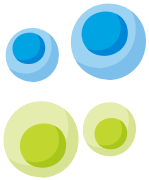
B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help eliminate pathogens as well as help other components of the immune system to function. Some remain as memory B cells to make the same antibody again later, if needed. Understanding of the role of B cells in eliminating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



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 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.

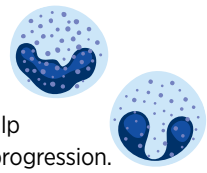


T cells help protect the body from infection and can also help fight cancer. Some remain as memory T cells to fight again later. There are two main types of T cells based on a type of protein present on their surface:

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

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.



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.

Source: (1).

marrow), organs (e.g., thymus), and the substances they make that help the body fight infections and other diseases, including cancer. The immune system actively detects threats from external (such as viruses and bacteria) and internal sources (such as abnormal or damaged cells) and works to eliminate them from the body.

The immune system is highly effective in detecting and eliminating cancer cells, a process also known as cancer immune surveillance (112). However, as cancer cells acquire new properties during the course of cancer development (see **Understanding the Path to Cancer Development**, p. 26), some cells find ways to "hide" from the immune system, such as by decreasing or eliminating the numbers and/or amounts of proteins on the surface of tumor cells that are used by the immune system to recognize cancer cells; triggering certain brakes on immune cells that prevent them from eradicating cancer cells; and releasing molecules that weaken the ability of immune cells to detect and destroy cancer cells (569). Ongoing research is focused on better understanding how tumor cells evade the immune system and leveraging this knowledge to develop novel cancer treatments.

Advances in understanding of how the immune system detects and destroys cancer cells in the human body has invigorated the field of cancer immunology and has firmly established immunotherapy as the fifth pillar of cancer medicine (570). 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 37**, p. 108).

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

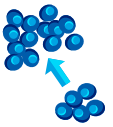
SIDEBAR 37

How Immunotherapeutics Work

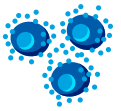
The way in which different immunotherapeutics unleash a patient's immune system to fight cancer varies:

Some **release the brakes** on the natural cancer-fighting power of immune cells such as T cells, for example, nivolumab (Opdivo) and pembrolizumab (Keytruda). These therapeutics are commonly known as immune checkpoint inhibitors.

Some **amplify the killing power of the immune system** by providing 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).



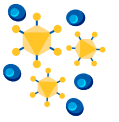
Some **increase the killing power of the immune system** by enhancing T-cell function, for example, interleukin-2 (Aldesleukin) and nogapendekin alfa inbakicept-pmln (Anktiva).



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, T cell-engaging bispecific antibodies such as blinatumomab (Blincyto).

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



Source: (1).

attacking cancer cells (see **Figure 18**, p. 109). These brakes are proteins on the surface of T cells and are called immune checkpoint proteins. Immune checkpoint inhibitors (ICIs) are a class of transformative new therapeutics that can release the brakes on T cells and trigger previously restrained T cells to attack and destroy cancer cells (83).

The use of ICIs in the treatment of cancer has rapidly expanded over the past decade and these therapeutics are considered one of the most exciting approaches to cancer treatment. This is in part because some patients with metastatic disease who have been treated with these therapeutics have had remarkable and durable responses. As one example, long-term results from a clinical trial testing the ICI pembrolizumab 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 (571). Recent analysis suggests that the use of ICIs is also favorably associated with patients' quality of life (572).

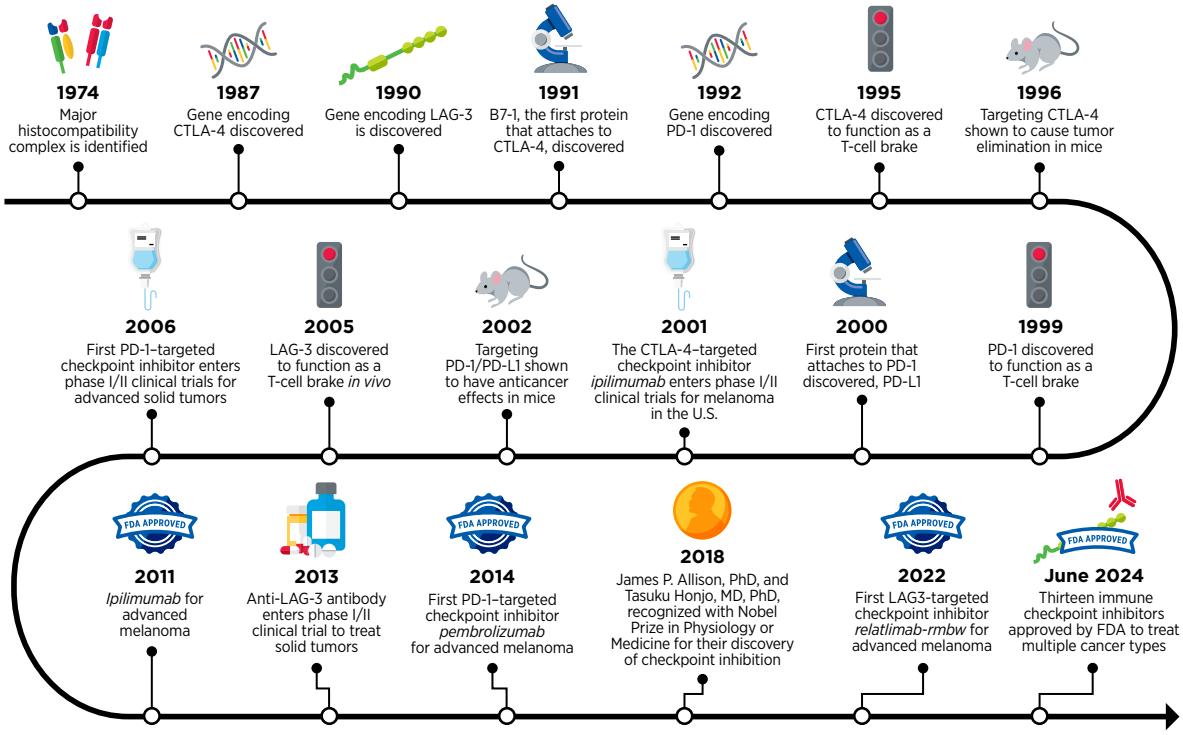
During the 12 months spanning this report (July 1, 2023–June 30, 2024), FDA approved two new ICIs—tislelizumab-jsgr (Tevimbra) and toripalimab-tpzi (Loqtorz)—and expanded the uses of two of the previously approved ICIs—durvalumab (Imfinzi) and pembrolizumab (Keytruda)—to treat additional cancer types. These approvals mean that, as of June 30, 2024, FDA has approved 13 ICIs, targeting one of three different T-cell brakes, CTLA-4, PD-1/PD-L1, or LAG-3. Additionally, these groundbreaking treatments are now approved for treating more than 20 cancer types as well as for treating any type of solid tumor characterized by the presence of certain molecular characteristics (see **Figure 19**, p. 110).

In October 2023, FDA approved a new PD-1–targeted ICI, toripalimab-tpzi, for the treatment of patients with nasopharyngeal carcinoma, a rare form of head and neck cancer with a high prevalence in certain parts of Asia. This is the first approval of an immunotherapeutic for this cancer. Toripalimab-tpzi was approved as an initial treatment for people with nasopharyngeal carcinoma that has come back or metastasized as well as for patients with recurrent or metastatic disease that has gotten worse despite standard chemotherapy.

FDA approval was based on the findings from two clinical trials that evaluated toripalimab-tpzi in patients with advanced nasopharyngeal carcinoma. In one trial, toripalimab-tpzi treatment shrank tumors or prevented them from growing in certain patients whose cancer had gotten worse despite previous treatment with standard chemotherapy. The second trial was a phase III clinical study which showed that patients treated with toripalimab-tpzi and chemotherapy lived for a median of 21.4 months without their cancer getting worse, compared to 8.2 months for those treated with chemotherapy

FIGURE 18

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



Immune checkpoint inhibitors (ICIs) are cancer immunotherapeutics that work by releasing certain "brakes" called immune checkpoint proteins on the surface of cancer-fighting immune cells. The first ICI to be approved by the US Food and Drug Administration (FDA) was ipilimumab, in March 2011. Ipilimumab targets an immune checkpoint protein on T cells, called CTLA-4. Several other ICIs target a second immune checkpoint protein called PD-1 and its binding partner, a protein called PD-L1. The first of these immunotherapeutics to be approved by FDA was pembrolizumab, in September 2014. Yet another checkpoint protein, called LAG-3, is the target of relatlimab-rmbw, an ICI that was approved by FDA in March 2022. Decades of basic, translational, and clinical research underpinned the development of these therapeutics, starting with the discoveries of the *CTLA-4*, *LAG-3*, and *PD-1* genes. Other milestones along the way to FDA approvals include the identification of the brake function of CTLA-4, LAG-3, and PD-1 proteins; the identification of binding partners that attach to and trigger the brake function; and the demonstration that ICIs targeting these brakes can eradicate cancer cells. While all the ICIs currently approved by FDA work on brakes located on T cells, ongoing research is evaluating the clinical utility of targeting brakes on additional immune cell types.

Source: (551).

alone (573). Additionally, overall survival after 3 years of starting treatment was 64 percent among patients treated with toripalimab-tpzi and chemotherapy compared to 49 percent for those treated with chemotherapy alone.

The approval of toripalimab-tpzi is a significant advance for patients with nasopharyngeal carcinoma, a cancer for which surgery is generally not a good option due to the location of the tumors and for which there is no standard treatment once the cancer has progressed after chemotherapy.

The second new ICI approved in the 12 months covered in this report is tislelizumab-jsgr (Tevimbra). In March 2024, it was approved for treating patients who have surgically inoperable or metastatic squamous cell carcinoma of the esophagus that has progressed despite cytotoxic chemotherapy. Although

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, 12 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, 2024, there was at least one ICI approved for treating more than 20 cancer types. In addition, there are several cancer types for which a deep selection of ICIs is available as a treatment option.

Source: (1).

esophageal cancer is rare—22,370 new cases expected in 2024 in the United States—it is one of the deadliest; the 5-year relative survival rate for patients diagnosed with the disease is just 22 percent (3). The approval of tislelizumab-jsgr was based on results from a phase III clinical trial in which it was shown that the ICI significantly improved overall survival compared with standard cytotoxic chemotherapy (574).

ICIs have yielded extraordinary benefits for many patients, but they can also have adverse effects, particularly the induction of autoimmune-like conditions. This occurs because ICIs release the brakes not only on cancer-fighting immune cells but also on some that recognize and injure normal tissues. To predict which patients are likely to experience adverse events and design treatments to combat these events without compromising the anticancer efficacy of the ICI, researchers must understand better why and how the adverse effects arise.

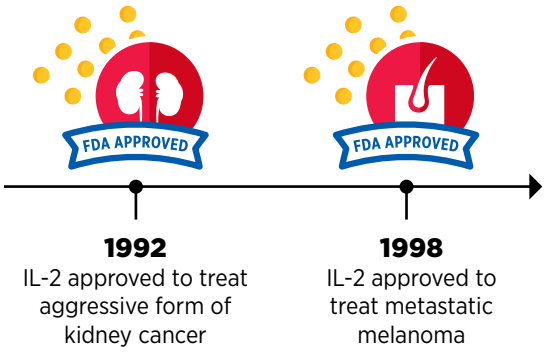
Identifying cellular and molecular markers that can predict whether ICIs are likely to work in a patient is an area of

extensive research investigation (575). Such biomarkers can help patients avoid unnecessary treatments and ICI-related toxicities including potential financial toxicities arising from high costs of these treatments (see **Challenges Faced by Survivors**, p. 130), and can also help avoid delaying potentially more effective treatments. Another important area of scientific inquiry is to identify behavioral and clinical factors, such as diet, physical activity, gut microbiome composition, and optimal combinations with other therapeutic modalities that can boost the efficacy of ICIs and increase the number of patients who respond favorably to these lifesaving treatments.

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 (576). While their use was initially limited to people with very advanced cancers that were no longer responding to standard treatments, ICIs are increasingly 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 (577,578). One area of extensive research is the use of these therapeutics before initial surgery, known as neoadjuvant treatment, in people with locally advanced cancers that are largely restricted to the tissue of origin.

Enhancing Immune Cell Function

Immune cells communicate with each other and with their surrounding cells through direct contact as well as through the release of a class of molecules called cytokines. Cytokines are also produced by nonimmune cells and play an essential role in rapidly activating the immune system in response to cellular stresses, such as infection, inflammation, and cancer (579).



Source: (581).

W35

For many decades, researchers have been investigating the natural ability of cytokines, such as interferons and interleukins, to boost the cancer-killing function of the immune system (580). Although cytokines have shown some promise, their success has been limited. One limitation is that cytokines do not persist very long in the body, so ongoing research is developing more stable versions of cytokines (581). Another challenge is the significant adverse effects when cytokines are given as a systemic treatment—treatment that is administered through the bloodstream and affects cells all over the body. Researchers are exploring ways to enhance the efficacy of cytokines while minimizing their side effects, for example, by delivering them in or near tumors (581).

FDA approval of nogapendekin alfa inbakicept-pmln (Anktiva) in April 2024 was a major advance in the field of interleukin-based cancer immunotherapy. Nogapendekin alfa inbakicept-pmln was approved for the treatment of adult patients with non–muscle-invasive bladder cancer (NMIBC) that did not respond to Bacillus Calmette-Guérin (BCG) treatment. The treatment is intended for patients with carcinoma *in situ*, which refers to very early cancer cells in the inner layer of the bladder lining, who may or may not also present with papillary tumors, which are unusual growths that start in the bladder lining and extend into the center of the bladder.

More than 83,000 new cases of bladder cancer will be diagnosed in the United States in 2024 (2). NMIBC—a type of bladder cancer that has grown through the lining of the bladder but has not yet invaded the muscle layer—makes up around 75 percent of all new cases of bladder cancer (583). Patients with high-risk NMIBC are usually treated with BCG—an immunotherapeutic that was originally developed as a vaccine against tuberculosis—which is instilled directly into the bladder. Although 80 percent of patients initially respond to BCG, over half of patients with an initial response experience recurrence and progression of cancer within a year, and many develop disease that no longer responds to BCG (584,585).

Patients who do not respond to BCG have very few treatment options other than surgical removal of the bladder. Although potentially curative, surgery is associated with high rates of complications. Additionally, many patients with underlying health conditions may be unwilling or unable to undergo surgery (585). Therefore, alternative treatments for patients with bladder cancer are an urgent medical need.

Nogapendekin alfa inbakicept-pmln is a mutated form of the cytokine interleukin (IL)-15 with potential immunomodulating and antitumor properties. It binds to the IL-15 receptor on immune cells, such as natural killer (NK) cells and CD8+ T cells (see **Sidebar 36**, p. 107), which activates the NK cells and T cells and boosts their multiplication, so they are better able to eradicate tumor cells. FDA approval was based on findings from a phase II/III clinical trial in which 62 percent of patients

SIDEBAR 38

T-Cell Based Adoptive Cell Therapy

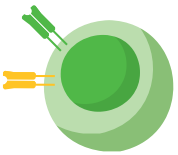
Adoptive T-cell therapy, also called cellular immunotherapy, dramatically increases the number of cancer-killing immune T cells, thus boosting a patient's immune system to seek and destroy cancer cells. It is a complex and multistep medical procedure. During the treatment, T cells are harvested from the patient to expand them in number and/or genetically modify them in the laboratory to enhance their cancer-fighting capabilities. The expanded and/or genetically enhanced T cells are then reinfused in the patient to help eliminate cancer cells.

Types of Adoptive T-Cell Therapy

There are three main types of adoptive T-cell therapy. As of June 30, 2024, two types, chimeric antigen receptor (CAR) T-cell therapy and tumor-infiltrating lymphocyte (TIL) therapy, have been approved by the US Food and Drug Administration (FDA). Afamitresgene autoleucel (Tecelra), a T-cell receptor (TCR) therapy, has been shown to be effective in patients with rare forms of sarcoma and awaits regulatory decision from FDA in August 2024 (588).

FOR 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.



FOR T-CELL RECEPTOR (TCR) T-CELL THERAPY

T cells are harvested from a patient's blood and genetically modified in the laboratory so that they have a synthetic protein called a TCR on their surface, which recognizes certain protein fragments on the surface of the patient's cancer cells. The genetically modified T cells are expanded in number and infused back into the patient. The TCR modification helps the T cells seek out the patient's cancer cells more effectively and triggers them to attack the patient's cancer cells.

FOR 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.

treated with nogapendekin alfa inbakicept-pmln experienced a complete response, which means no cancer cells could be detected in their urine and in the urinary bladder tissue. Among patients who had a complete response, the response lasted for at least 12 months in 58 percent of patients and at least 24 months in 40 percent of patients (586).

Boosting the Cancer-killing Power of Immune Cells

Research has shown that immune cells, such as T cells, are naturally capable of destroying cancer cells. It has also shown that in patients with cancer, there are often insufficient numbers of cancer-killing T cells, and that the cancer-killing T cells that are present are unable to find or destroy the cancer cells for one of several reasons. This knowledge has led researchers to identify several ways to boost the ability of T cells to eliminate cancer cells.

Adoptive cell therapy (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 (587). While many of the adoptive cell therapies currently in late-stage clinical development and all that are approved by FDA utilize patient-derived T cells (see **Sidebar 38**, p. 112), ongoing research is looking to harness the cancer-killing power of other types of immune cells, including NK cells and macrophages. Chimeric antigen receptor (CAR) T-cell therapy is one type of ACT that has generated enormous excitement in cancer medicine in recent years. This is because treatment with CAR T cells has demonstrated unprecedented efficacy in certain patients with very advanced leukemia or lymphoma.

Like ICIs, CAR T-cell therapy is the culmination of decades of basic, translational, and clinical research utilizing knowledge of the cellular and molecular components of the immune

SIDEBAR 39

CAR T-cell Therapies Approved by the US Food and Drug Administration

As of June 30, 2024, there are six distinct FDA-approved CAR T-cell therapies to treat different cancer types:

Approval year	Therapy name	Treatment for
2022	Ciltacabtagene autoleucel (Carvykti)	Adult patients with relapsed or refractory multiple myeloma
2021	Idecabtagene vicleucel (Abecma)	Adult patients with relapsed or refractory multiple myeloma
2021	Lisocabtagene maraleucel* (Breyanzi)	Adult patients with certain types of B-cell lymphoma
2020	Brexucabtagene autoleucel* (Tecartus)	Patients with relapsed or refractory mantle cell lymphoma
2017	Tisagenlecleucel* (Kymriah)	Adult patients with certain types of B-cell lymphoma and young adult patients up to age 25 with certain types of lymphoblastic leukemia
2017	Axicabtagene ciloleucel* (Yescarta)	Adult patients with certain types of B-cell lymphoma

*These therapeutics have received expanded approvals for the treatment of additional blood cancer types since their first approvals by FDA.

system, genetic engineering, and the biological underpinnings of blood cancers. As of June 30, 2024, six CAR T-cell therapies have been approved by FDA, all for the treatment of blood cancers, including lymphoma, leukemia, and, most recently, multiple myeloma (see **Sidebar 39**, p. 113). Collectively, these treatments have transformed the lives of adult and pediatric patients with blood cancers (589). As one example, based on a recent analysis, axicabtagene ciloleucel (Yescarta), which was also approved by FDA in 2017, is the first treatment in nearly three decades to improve overall survival in relapsed or refractory large B-cell lymphoma (590).

Generating CAR T cells is a complex procedure that can only be performed at specially certified health care facilities by highly trained medical professionals, which may reduce access to this therapy. Additionally, like other cancer treatments, CAR T-cell therapies can cause side effects, some of which can be potentially life-threatening. Moreover, recent studies show that certain CAR T-cell therapies may even be linked to secondary cancers (591,592). Another issue that researchers are trying to address is the fact that CAR T-cell therapies have so far proven less successful against solid tumors. Developing simpler and safer ways to bring the promise of this class of immunotherapeutics to more patients with different cancer types is an area of 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 would be readily available for use rather than manufactured for each patient.

While clinical research has been long evaluating the efficacy of three different types of adoptive T-cell therapy (see **Sidebar 38**, p. 112) prior to 2024 only CAR T-cell therapy was approved by FDA. This changed in February 2024 with FDA approval of lifileucel (Amtagvi), the first cancer immunotherapeutic that uses tumor-infiltrating lymphocytes (TILs).

Like CAR T cells, TILs are manufactured using a patient's own T cells (see **Sidebar 38**, p. 112). However, a key difference is that unlike CAR T cells, which are derived from T cells in the patient's blood, TILs are collected from a patient's tumor. The second major difference is that unlike CAR T cells, which are engineered to recognize and kill cancer cells, TILs are not genetically modified in the laboratory because these cells are already capable of recognizing and finding their way to tumors as evident from the fact that they were isolated from the tumors themselves. TILs recognize cancer cells based on the presence of specific abnormal

proteins, or antigens, on their surface. Once collected from a patient's tumor, TILs are treated with the cytokine IL-2 to expand them in numbers before they are infused back into the patient.

Lifileucel was approved for patients with advanced melanoma that has gotten worse after treatment with ICIs or molecularly targeted therapeutics and is the first cellular immunotherapy to be approved for a solid tumor. FDA approval was based on a clinical trial in which the tumors shrank or disappeared in more than 31 percent of patients after treatment with lifileucel (593,594). Of the patients who responded to lifileucel, more than half lived at least a year without any evidence of their cancer getting worse. Following the treatment, some patients experienced adverse events, which were mostly transient and manageable by their clinical care team.

Up until now, patients with advanced melanoma, such as **Jennifer Ficko** (see p. 117), whose disease progressed after treatments with ICI and/or molecularly targeted therapeutics, such as BRAF/MEK inhibitors, had no effective therapeutic options. The FDA approval of lifileucel in this subset of patients fulfills a major unmet medical need.

Directing the Immune System to Cancer Cells

An immune cell must find a cancer cell before it can attack and eliminate it. Many therapeutic antibodies approved by FDA for the treatment of cancer work, at least in part, by helping immune cells find cancer cells. Because of the effectiveness and promise of antibody-based immunotherapeutics, researchers have been working to develop new and improved versions of this important class of anticancer therapeutics.

T cell-engaging bispecific antibodies are one class of anticancer therapeutics that are moving rapidly from the laboratory to clinical practice. Using two or more arms that are engineered into these antibody particles, these immunotherapeutics bind to immune cells and cancer cells simultaneously. By acting as a connector, T cell-engaging bispecific antibodies bring cancer cells into close proximity with T cells, which are then activated and eliminate the cancer cells.

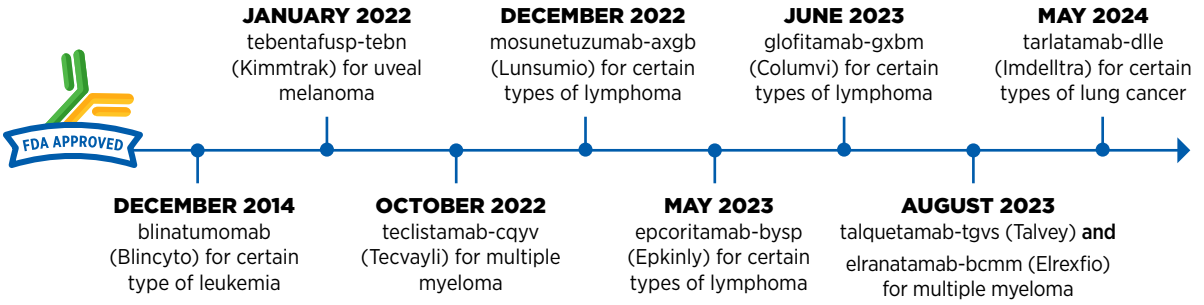
Therapeutic antibodies are used in the treatment of numerous cancer types and can function in several different ways.

W36

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 (595). Unprecedented advances in genetic engineering, molecular biology, and immunology over the past decade have led to a rapid proliferation in this innovative new area of cancer medicine. Between July 1, 2023, and June 30, 2024, FDA approved three new T cell-engaging bispecific antibodies for the treatment of multiple myeloma and lung cancer.

Two of the T cell-engaging bispecific antibodies approved during the 12 months covered in this report were for treatment of patients with multiple myeloma, one of the most common blood cancers in the United States. An estimated 35,780 new cases are expected to be diagnosed in 2024 and 12,540 people will succumb to the disease (3). The burden is disproportionally higher in the Black population (3). In recent years, the development and FDA approval of new therapeutics—including proteasome inhibitors like bortezomib (Velcade) and carfilzomib (Kyprolis), immunomodulatory agents like lenalidomide (Revlimid)

As of June 30, 2024, FDA has approved nine T cell-engaging bispecific antibodies for the treatment of cancer. Some of these therapeutics have received expanded approvals for the treatment of additional cancers since their first approval.



Source: (596).

W37

and pomalidomide (Pomalyst), and immunotherapeutics like the CD38-targeted daratumumab (Darzalex)—have improved outcomes for patients. Despite these advances, unfortunately, many patients whose disease initially responds to the new therapeutics eventually experience relapse owing to treatment resistance.

In August 2023, FDA approved two T cell-engaging bispecific antibodies, talquetamab-tgvs (Talvey) and elranatamab-bcmm (Elrexfio), for adult patients with multiple myeloma that have relapsed after, or never responded to, at least four prior lines of therapy. Both antibodies attach to a molecule called CD3 on T cells with one arm. With the second arm, talquetamab-tgvs attaches to a protein, G protein–coupled receptor, family C, group 5, member D (GPRC5D), and elranatamab-bcmm attaches to a protein called B-cell maturation antigen (BCMA). Both GPRC5D and BCMA are present at high levels on the surface of most multiple myeloma cells. By attaching to these molecules on T cells and myeloma cells, the T cell-engaging bispecific antibodies bring the two cell types together, directing the T cells to home in on the myeloma cells. As a result, T cells are activated, and they destroy the adjacent myeloma cells.

Talquetamab-tgvs is the first FDA-approved therapeutic that targets GPRC5D and has been transformative for patients such as **Vicki W. Jones** (see p. 119). The approval was based on a clinical trial in which patients received either 0.4 mg/kg or 0.8 mg/kg of the therapeutic subcutaneously, following step-up doses, until disease progression or unacceptable toxicity. Step-up dosing is an approach used in the treatment with T cell-engaging bispecific antibodies whereby the dose administered to a patient is raised incrementally before reaching the target dose level. This helps the body's immune system to be primed gradually, thereby reducing the risk of severe immune-related adverse events. Among both groups, receiving either 0.4 mg/kg or 0.8 mg/kg of the therapeutic, more than 70 percent of patients responded to the treatment (597).

The approval of elranatamab-bcmm was based on a clinical trial in which nearly 58 percent of patients responded to the therapeutic. This is the second FDA approval of a BCMA-targeted T cell-engaging bispecific antibody for patients with multiple myeloma who have received at least four prior lines of therapy. The first, teclistamab-cqyv (Tecvayli), was approved in October 2022 (1). Historically, multiple myeloma that has progressed following multiple classes of treatment has been extremely challenging to treat. Therefore, recent approvals of talquetamab-tgvs (Talvey) and elranatamab-bcmm (Elrexfio) bring hope to patients by providing them with new and effective treatment options.

About 10 to 15 percent of all lung cancer cases are small-cell lung cancer (SCLC). SCLC is a fast-growing, aggressive disease associated with poor outcomes. In the United States, overall incidence of SCLC has been declining since its peak in the 1980s (598). However, incidence has increased among women and there has been little improvement in survival outcomes.

Most patients with SCLC are diagnosed with extensive-stage disease, which means the cancer has spread beyond the lung and the area between the lungs to other lymph nodes or other parts of the body. Although most patients may respond to treatments initially, their cancers usually progress within months. Patients at this stage have limited options, and their overall survival rarely exceeds 8 months (599). Therefore, FDA approval of tarlatamab-dlle (Imdelltra) in May 2024 for extensive-stage SCLC with disease progression on or after chemotherapy is a major clinical advance for this patient population.

Tarlatamab-dlle is a T cell-engaging bispecific antibody that binds CD3 on T cells and the protein delta-like ligand 3 (DLL3) on lung cancer cells, leading to T-cell–mediated killing of cancer cells. DLL3 is abnormally expressed on the surface of SCLC cells in 85 percent to 94 percent of patients with SCLC, making it a suitable target for therapeutic intervention (599). FDA approval was based on a phase II clinical trial in which tarlatamab-dlle shrank tumors in 40 percent of the patients who received the treatment (599). In more than 50 percent of patients whose tumors shrank with tarlatamab, the therapeutic kept the cancer at bay for at least 6 months.

It is important to note that immunotherapeutics, including CAR T cells, ICIs, and T cell-engaging bispecific antibodies, may cause serious adverse side effects, some of which could be life-threatening if not managed immediately and appropriately by trained medical professionals. In fact, FDA approvals of all three T cell-engaging bispecific antibodies discussed above come with a warning of life-threatening adverse events, such as cytokine release syndrome and neurologic toxicity. Because of these risks, talquetamab-tgvs and elranatamab-bcmm are available only through a restricted program, called the Risk Evaluation and Mitigation Strategy (REMS).

★ SPOTLIGHT

Research-driven Progress Against Childhood and AYA Cancers

In the United States, an estimated 9,620 children (ages 0 to 14 years) and 84,100 adolescents and young adults (AYA) (ages 15 to 39 years) will be diagnosed with cancer in 2024. There has been enormous progress in the

continued on page 120

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

Jennifer Ficko

Pooler, Georgia

Jennifer Ficko was diagnosed with stage IV melanoma in 2010 at the age of 48. The next 7 years were an ongoing battle that tested her in ways she would have never expected. Thanks to research-driven breakthroughs in cancer science and medicine, Jennifer was able to participate in a clinical trial evaluating an immunotherapeutic that used her own immune cells against her cancer. She responded positively to the treatment. "And now, almost 15 years later, I am 7 years cancer free," Jennifer said.

> "Many cancers are on the rise. We need research so that we can find cures, or perhaps prevent [cancers] from occurring in the first place. This can only be accomplished through funding for cancer research. We must have congressional support."

Jennifer's journey with cancer began with a seemingly harmless tumor on the side of her head. She remembers having it for years, but every doctor she saw dismissed it as nothing serious. It was not until she mentioned it to her trusted ear, nose, and throat specialist that things took a turn. He recommended removing the tumor, as it had started to itch, but neither he nor Jennifer expected the diagnosis that followed. "Two days before Thanksgiving, he called me to say that I had melanoma."

The shock of the diagnosis was compounded by the fact that her 16-year-old son overheard the conversation. Jennifer and her husband, stunned and scared, turned to the Internet to understand what melanoma really meant. What they found was bleak. Her local doctors in Fairfield, Connecticut offered no hope, essentially telling Jennifer that her time was limited.

Thanks to her job at a large company with extensive medical connections, Jennifer was referred to specialists at Memorial Sloan Kettering Cancer Center. The team there referred her to Smilow Cancer Hospital, where she could receive the same treatments closer to home. "I had surgery a couple days before Christmas," she said. The surgeon took out the tumor and several lymph nodes, which revealed that the cancer had spread.

Jennifer enrolled in a clinical study that was evaluating the immune checkpoint inhibitor ipilimumab (Yervoy), a novel treatment at the time. Unfortunately, Jennifer did not respond to the treatment, and went on to receive a combination of ipilimumab with another checkpoint inhibitor, nivolumab (Opdivo). While she had an intermittent response with the combination, Jennifer experienced numerous severe side effects including a detached retina, hearing loss, hypothyroidism, and others. But Jennifer pushed through.

The turning point came in 2017. Running out of options, Jennifer took the recommendation from her oncologist, Dr. Harriet Kluger, to participate in a clinical trial at Yale Cancer Center. The trial was evaluating a novel immunotherapy known as tumor-infiltrating lymphocyte (TIL) therapy. The researchers isolated immune cells known as T cells from her tumor, grew them in numbers, and infused them back in her body. The treatment was brutal. Jennifer's body responded with a severe reaction. "My throat closed. I couldn't breathe. My poor husband who came in the middle of this must have thought I was dying," Jennifer said.

But it was also a sign that the treatment was working. "The tumor swelled because all those immune cells were getting stimulated and invading her tumor," said Dr. Kluger. Shortly after, the tumors began to shrink, and slowly, Jennifer began to recover.

The road to recovery was long and exhausting. For months, she lay on the couch, barely able to move, her husband by her side, force-feeding her to keep her strength up. But with time, Jennifer regained her strength, and continued to be cancer free.

Now at 61, Jennifer reflects on the journey that brought her to where she is today. Despite the lingering side effects, and the daily medication she must take, she considers herself lucky. She has had the chance to watch her children grow into successful adults, both pursuing careers in medicine, perhaps inspired by their mother's battle.

Jennifer talks about the power of resilience and the importance of keeping a positive attitude. Even in the darkest moments, she refused to let cancer define her. She saw it as an inconvenience, something she had to get through, and with the support of her family, she did. Her message is clear: Cancer is tough, but with the right attitude, support from friends and family, and the advances in medical research, it does not have to be a death sentence.

As she continues to live her life, Jennifer remains grateful for the opportunities she has had and the life she continues to live. Her story is a testament to the vital importance of medical research. "I was lucky. Not everybody is so lucky," she said. "Many cancers are on the rise. We need research so that we can find cures, or perhaps prevent [cancers] from occurring in the first place. This can only be accomplished through funding for cancer research. We must have congressional support; otherwise we'll never find a cure."

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

Vicki W. Jones

Spokane, Washington

Vicki W. Jones never thought she would have cancer. Even though Vicki's mother and grandfather died of cancer, they were in their 80s and were both smokers. Vicki, on the other hand, never smoked. So, it was a complete shock when she was diagnosed with multiple myeloma—a cancer she had never heard of—at the age of 51.

Before the diagnosis, life was good. Vicki had an exciting new job. She had a complete health checkup when she turned 50; everything seemed perfect. A year later, when Vicki went back for a regular checkup, the doctor noted that her "protein levels were high." She thought it was probably because she had been on a high-protein diet, but her doctor insisted she see a hematologist. "The first inkling I had that something could be wrong was when I drove up to the building where the hematologist was located and it said Cancer Care Northwest," Vicki recalled. After a few tests, Vicki was diagnosed with multiple myeloma on June 18, 2004.

"My husband and I were together in the clinic when the hematologist broke the dreaded news. I had never heard of multiple myeloma, but he said that 51% of people with that diagnosis were still alive after 5 years. And I thought, still alive, but in what shape? Are they bedridden? Are they in miserable pain? Do they wish they were dead?" Vicki recalled.

"So I went home and prepared to die," she continued. In preparation for the worst-case scenario, Vicki and her husband started to draw up a will and Vicki had to decide who would get her favorite possessions. "It was really sad to think that I would never know what it would be like to be an old woman," Vicki remembered.

> "There are two words I use all the time. One is 'progress;' the other is 'progression.' I am lucky that progress in cancer research has been faster than the progression of my disease."

Nonetheless, Vicki started chemotherapy, which was the only treatment option available to patients with multiple myeloma at that time. "It made me lose all my hair. I was an emotional train wreck. I am really glad that my husband was there to support me," Vicki said. Despite all the side effects, chemotherapy worked. In about 3 months or so, Vicki stopped chemotherapy and, later, underwent a stem cell transplant. However, she only had a partial response and her cancer relapsed.

For the next several years, Vicki received many treatments. "I would be on a drug, and it would work really well. But I would slowly relapse. Fortunately, a new drug would become available. This kept happening over and over. Every relapse was met with a newly approved treatment. Not everybody responds to everything, but I responded to each of them, which is really lucky. And even though I never had complete remission, my response to different drugs lasted from 1 year to 4 years and they kept me going that much longer," Vicki said.

Vicki has been studying myeloma ever since her disease was diagnosed. She read everything on myeloma, asked the doctor every question she could think of, attended every seminar, and watched every webinar. Now, Vicki is a myeloma coach for the HealthTree Foundation, where she helps other people with myeloma cope with the disease. In 2019, at a scientific meeting, Vicki learned about talquetamab, a new immunotherapeutic that was in early testing.

"I followed the development of this drug for the next several years. As the studies went on and results came in, it seemed to work really well. I was on belantamab mafodotin-blmf, which worked for some time, but my cancer eventually relapsed. I suggested talquetamab to my doctor," Vicki recalled.

Since October 2023, Vicki has been receiving talquetamab. Because talquetamab can cause serious side effects, Vicki had to be in the hospital and monitored carefully for 10 days. Fortunately, Vicki didn't have any side effects. "I made popcorn at night and watched movies. It was a relaxing stay. But I don't want to downplay the seriousness of possible side effects because they can be life threatening," Vicki cautioned. "Also, talquetamab is really difficult to get in a community setting. It is awful to think that people who live in remote areas and might need this drug do not have access to it."

Vicki has had some side effects from her treatments over the years. "Some days, myeloma is a physical challenge, and some days it's a mental challenge. Although I have not experienced very bad side effects from treatments, my bones did become fragile. I have had some broken ribs. I've also had some fatigue, weight gain, weight loss, blurred vision, loss of taste, and difficulty swallowing, but nothing that I could not deal with. I have been on talquetamab 10 months now, and I'm just starting to get my sense of taste back," Vicki said.

Living with cancer for more than 20 years has given Vicki an amazing outlook. "There are two words I use all the time. One is 'progress'—that's what cancer research is making, which is wonderful. The other is 'progression,' which is what my disease is always doing, which is horrible. I am incredibly lucky that progress in cancer research has been faster than the progression of my disease. Without that I wouldn't be here. And, I am so grateful.

Oh, and about my initial remorse over not getting to grow old. When I catch myself in the mirror, I'm shocked to see what I look like. But I have to say, I love every wrinkle and every gray hair because I am still here! Against the odds I'm still alive! I am loving life. I want to keep doing that."

Vicki's message to lawmakers and policymakers is straightforward: "I work really hard to live well with cancer. I might even make it look easy. But trust me, you do not want this for yourself or your loved ones. I know there are some in Congress who know this firsthand. So I truly hope you will do everything you can to fund cancer research. We've already got the momentum. So many things have improved in the last 20 years. We're making progress. We can't let that stop. We can eradicate this beastly disease."

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. However, some cancers such as bone sarcomas or certain brain tumors have been difficult to treat and continue to have poor survival.

Many of the initial advances in the treatment of childhood cancers were made through intensification of cytotoxic chemotherapeutics, which, while effective, were associated with significant toxicities, including short- and long-term adverse effects (600). With greater understanding of the biology of childhood and AYA cancers and innovations in technology, there is an increasing focus on identifying therapeutic vulnerabilities in historically intractable cancers and utilizing personalized approaches to target these diseases as well as on reducing treatment intensities among patients with curable cancers who have a favorable prognosis, to improve their quality of lives (601). Research shows that cutting-edge technologies such as gene sequencing can improve clinical care of children with cancer by informing personalized treatment options (602). Researchers are also refining the use of traditional treatments, such as using novel formulations or newer delivery methods for cytotoxic chemotherapeutics to reduce toxicities.

One of the drivers of progress against cancer in children is that the enrollment of children (14 and younger) in clinical trials has been historically much higher compared to that of adult patients (603). Enrollment rates of childhood cancer patients from racial and ethnic minority groups in clinical trials supporting FDA approval of cancer treatments are also higher than that of their adult counterparts (604). These differences are partly attributable to the fact that most children with cancer are treated at specialized pediatric cancer centers that offer access to clinical trials. However, recruitment of AYA patients with cancer has been an ongoing challenge (605) and needs additional efforts.

Similar to what has been highlighted in the prior 13 editions of the annual *AACR Cancer Progress Report*, FDA has made numerous decisions in the 12 months covered in this report that will continue the momentum of progress against pediatric and AYA cancers (606).

Advances in the Treatment of Leukemia

Leukemias are the most common cancers among US children and adolescents. B-cell acute lymphocytic leukemia (ALL) is the most common cancer diagnosed among children ages 0 to 14 in the United States. The 5-year survival for children and adolescents is greater than 90 percent, attributable to spectacular advances in risk stratification at diagnosis with treatment escalation for those with high risk of relapse as well as to the new and improved treatment options that are now available in the clinic. Decades of basic, translational, and clinical research have enhanced our knowledge of the underpinnings of leukemia as well as that of the immune system. Researchers are harnessing this knowledge to develop personalized treatments including immunotherapeutics and molecularly targeted therapeutics that target ALL.

As one example, in 2017, the first CAR T-cell therapy tisagenlecleucel (Kymriah) was approved by FDA 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. This revolutionary immunotherapeutic has allowed some patients 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 (607). Additionally, more than 50 percent of patients were living without their disease coming back at the end of three years after treatment completion, suggesting that CAR T cells can lead to durable cancer control.

The T cell-engaging bispecific antibody blinatumomab, which was initially approved in 2014 for the treatment of adults with B-cell ALL, received expanded approval by FDA in 2017 for the treatment of children whose ALL had returned following at least one course of treatment. Clinical studies show that in children and AYAs with B-cell ALL that had relapsed, treatment with blinatumomab led to better outcomes and fewer side effects compared to chemotherapy alone (608,609). Moreover, the addition of blinatumomab to chemotherapy appears to be highly efficacious for infants with newly diagnosed ALL with certain genetic alterations known as KMT2A-rearrangement, a disease historically associated with poor outcomes (610).

Antibody-drug conjugates are an emerging class of molecularly targeted therapeutics that use an antibody to deliver an attached cytotoxic chemotherapeutic directly to the cancer cells that have the antibody's target on their surfaces. Once the antibody attaches to its target on the surface of a cancer cell, the antibody-drug conjugate is internalized by the cells. This leads to the chemotherapeutic being released from the antibody and killing the cancer cell. The precision of antibody targeting reduces the side effects of the chemotherapeutic compared with traditional systemic delivery.

CHRONIC MYELOID LEUKEMIA (CML)
ACCOUNTS FOR ONLY
3% OF ALL CHILDHOOD LEUKEMIAS.

The molecularly targeted therapeutic bosutinib (Bosulif), which is approved for adults with CML, was **approved in September 2023 for pediatric patients with CML** that has certain biomarkers and that is newly diagnosed or resistant or intolerant to prior therapy. W38

Inotuzumab ozogamicin (Besponsa) is an antibody-drug conjugate comprising a CD22-targeted antibody linked to the chemotherapeutic calicheamicin. It was approved for treating adults with B-cell ALL in August 2017. Subsequent studies have shown that inotuzumab ozogamicin is also effective in children and adolescents. Based on findings from a clinical trial in which 42 percent of patients who received inotuzumab ozogamicin achieved a complete remission, meaning they had no evidence of cancer, in March 2024, FDA approved the therapeutic for pediatric patients 1 year and older with CD22-positive B-cell ALL that has relapsed or stopped responding to treatments.

Patients who receive inotuzumab ozogamicin may need a stem cell transplant to ensure durable cancer remission. While treatment with inotuzumab ozogamicin increases the risk of developing serious liver toxicities in certain patients, it increases treatment options for a group of ALL patients who may be ineligible for CAR T-cell therapy and have no remaining options.

Advances in the Treatment of Brain Tumors

Brain and other nervous system tumors are the second most diagnosed cancers in children. Low-grade glioma is the most common type of brain tumor in children. These are slow-growing tumors that can often be cured with surgery alone. However, depending on their location in the brain, some low-grade gliomas cannot be fully removed, for example, if they are adjacent to vital structures in the brain. Additionally, in some cases low-grade gliomas may grow back even after a complete surgical removal. Traditionally, most children whose tumors are not surgically removable or have come back after surgery receive chemotherapeutics. While chemotherapies can be effective, they are associated with substantial side effects. Therefore, alternative treatments for these children are an urgent need in cancer medicine.

Research has demonstrated that alterations in the *BRAF* gene leading to aberrant activation of the BRAF protein signaling pathway are common in pediatric low-grade gliomas. The BRAF protein has a critical role in controlling cell growth. The *BRAF* gene is altered in approximately 6 percent of all human cancers (402). Most cancer-related changes in the *BRAF* gene cause the protein to continuously stay active, thus helping cancer cells grow faster than normal cells. Common cancer-related changes in the *BRAF* gene include structural variations such as *BRAF* gene fusions or rearrangements and/or single base changes such as the *BRAF* V600E mutation (see **Table 2**, p. 40). *BRAF* structural variations are more common than *BRAF* V600E mutations in children and adolescents with low-grade gliomas.

A combination of two molecularly targeted therapeutics that target the BRAF pathway, dabrafenib (Tafinlar) and trametinib (Mekinist), was approved by FDA in March 2023 for children with low-grade glioma that has a *BRAF* V600E mutation. The combination therapy, however, does not work in patients such as **Michael Methner**, p. 125 who have *BRAF* gene fusions or rearrangements. Therefore, FDA approval of tovorafenib (Ojemda) in April 2024 for patients 6 months and older with relapsed or treatment-unresponsive low-grade glioma that has a *BRAF* fusion or rearrangement or *BRAF* V600 mutation brings hope to many more parents and families whose children are diagnosed with the disease. The approval was based on a clinical trial in which tumors shrank or disappeared entirely in almost 70 percent of children treated with tovorafenib (611).

Researchers are now investigating whether tovorafenib in combination with chemotherapy could be used earlier on during the course of treatment as the initial therapy for children with low-grade gliomas that have fusions, rearrangements, or other mutations in the *BRAF* gene. Additionally, ongoing investigation is evaluating a separate molecularly targeted therapy, selumetinib (Koselugo), as the initial treatment after surgery for children with low-grade glioma regardless of their BRAF status. Selumetinib blocks the function of a protein called MEK, which is part of the same growth-promoting signaling pathway as BRAF. The therapeutic was approved by FDA in 2020 for the treatment of a different childhood cancer known as NF1–related plexiform neurofibroma.

Researchers are also exploring new and improved therapeutic options for children with more aggressive forms of brain tumors. As one example, clinical studies are examining CAR T-cell therapy in some children and young adults with a fast-growing, highly aggressive brain tumor called diffuse intrinsic pontine glioma

(DIPG) (612). The CAR T cells which, in this case, target a tumor-associated glycolipid (lipid attached to a carbohydrate) on the surface of DIPG cells, called GD2, are administered in small doses and infused directly into the brain. Initial findings from the study reported positive responses in terms of reductions in tumor size as well as improvements in cancer-related symptoms.

Advances in the Treatment of Solid Tumors Outside the Brain

Neuroblastoma is the most common extracranial solid tumor in children. Researchers use patient factors (age at diagnosis, disease stage) and tumor genetics to predict the likelihood of a child with neuroblastoma to be cured and decide treatments accordingly. While children with high-risk disease have had poorer outcomes historically, research-driven clinical breakthroughs in recent years have made major strides in the clinical care for these patients.

As one example, decades of basic, translational, and clinical research, starting from the recognition of the molecule GD2 as a tumor-associated glycolipid in 1984, led to the development of dinutuximab (Unituxin), an immunotherapeutic, that was approved in 2015 for treating children with high-risk neuroblastoma. Dinutuximab works by attaching to GD2 on neuroblastoma cells and flagging them for destruction by immune cells, using a natural process called antibody-dependent cellular cytotoxicity. Recent data demonstrate that dinutuximab is extending lives for many children with high-risk neuroblastoma (613). Since the approval of dinutuximab in 2015, FDA has approved a second therapeutic, naxitamab-gqgk (Danyelza), which works similarly to dinutuximab, for the treatment of patients with neuroblastoma.

Despite recent advances, only around 50 percent of children with high-risk neuroblastoma survive 5 years or longer. Patients whose cancer has come back have a poor outcome, with a 5-year overall survival of less than 10 percent (614). Therefore, additional treatment options are still needed. In this regard, in December 2023, FDA approved the first therapeutic intended to reduce the risk of relapse in children with high-risk neuroblastoma such as **Parker Shaw**, p. 127. The treatment, eflornithine (Iwilfin), was approved for adult and pediatric patients with high-risk neuroblastoma with at least a partial response to prior therapies, including anti-GD2 immunotherapy.

Eflornithine blocks the function of a protein named ornithine decarboxylase, which has a high activity in tumor cells and promotes tumor cell multiplication. FDA approval was based on findings from a clinical trial that compared outcomes of patients who were treated with either eflornithine along with current standards of care or the standard of care alone as maintenance treatment after the initial therapy for high-risk neuroblastoma. The data from the trial showed a reduction in the risk of cancer relapse and improved overall survival in patients who received the eflornithine regimen (614).

Gastroenteropancreatic neuroendocrine tumors are extremely rare in children and have few available treatment options. In April 2024, the US Food and Drug Administration (FDA) approved **lutetium Lu-177 dotatate** for certain pediatric patients with gastroenteropancreatic neuroendocrine tumors. This is the **first FDA approval of a radiopharmaceutical for this condition in children.**

W39

Advances in cancer treatment are also benefiting childhood and AYA patients with rarer forms of solid tumors. As one example, in December 2022, the ICI atezolizumab (Tecentriq) became the first treatment to be approved by FDA for the treatment of patients with alveolar soft part sarcoma (ASPS), an extremely rare cancer that mainly affects AYAs. According to NCI, about 80 people are diagnosed with the disease in the United States each year. ASPS is a slow-growing cancer that forms in soft tissues such as muscle, fat, or nerves. Although the tumor grows slowly, once metastatic, ASPS has poor outcomes.

Chemotherapeutics have limited benefit and molecularly targeted therapeutics do not have lasting effectiveness against ASPS. FDA approved atezolizumab for the treatment of ASPS that has spread to other parts of the body or cannot be removed by surgery. The approval was based on findings from a clinical trial which showed that treatment with atezolizumab either led to tumor shrinkage or kept the disease at bay (615) and represents a significant advance for a rare disease.

Advances in Biomarker-based Treatments

Characterization of genetic alterations that drive tumor growth has been instrumental in understanding tumor biology and conducting genetically informed clinical

trials such as basket, umbrella, and platform clinical trials (see **Clinical Research**, p. 79). These advances have accelerated the pace of development and FDA approval of molecularly targeted therapeutics and immunotherapeutics that are effective against cancers originating at different sites in the body but share biological underpinnings. In fact, one of the most notable achievements in precision medicine was the first FDA approval of a molecularly targeted therapeutic to treat cancer based on the presence of a specific genetic biomarker in the tumor irrespective of the site at which the tumor originated. The therapeutic, larotrectinib (Vitrakvi), was approved by FDA in 2018 for treating children and adults who have solid tumors that test positive for the *NTRK* gene fusions.

Since the approval of larotrectinib, two additional molecularly targeted therapeutics, entrectinib and repotrectinib, have been approved by FDA for treating children with solid tumors based on the same *NTRK* gene fusion biomarker (see **Figure 20**, p. 128). The approvals of larotrectinib, entrectinib, and repotrectinib for use in a tissue-agnostic way followed several decades of basic, translational, and clinical research (see **Figure 20**, p. 128).

These therapeutics work by targeting three related proteins called TRKA, TRKB, and TRKC. The genes *NTRK1*, *NTRK2*, and *NTRK3* provide the code that cells use to make these proteins. Genetic alterations known as structural variations that involve the three *NTRK* genes and lead to the production of *NTRK* gene fusions, and subsequently to TRK fusion proteins, drive the growth of several cancer types that occur in adults and children, including rare cancers such as soft tissue sarcomas. Overall, researchers estimate that *NTRK* gene fusions fuel the growth of up to 1 percent of all solid tumors.

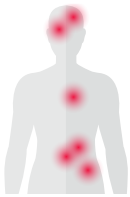
The recent approval of repotrectinib in June 2024 for children 12 years and older and adults was based on findings from a clinical trial that evaluated the therapeutic in patients who had or had not received a prior TRK-targeted therapy. The study showed that the tumors shrank in nearly 60 percent of patients who had not received a prior TRK-targeted therapy and in half of patients who had received a prior TRK-targeted therapy.

Mutations in the *RET* gene, including single base changes, structural variations, and deletions that lead to abnormal activation of the RET protein, are rare alterations observed mostly in patients with certain types of thyroid cancer and lung cancer (616). In children and AYA patients, *RET* mutations are frequently reported in papillary thyroid carcinomas and medullary thyroid cancers and less frequently in glioma, lipofibromatosis, inflammatory myofibroblastic tumor, and infantile myofibromatosis (617).

A RET-targeted therapeutic, selpercatinib, was approved by FDA first in 2020, for lung and thyroid cancers with *RET* mutations and then in 2022 in a tumor-agnostic manner for the treatment of adult patients with advanced solid tumors with a *RET* mutation. Most recently, in May 2024, FDA has approved selpercatinib for the treatment of pediatric patients 2 years and older with metastatic thyroid cancer or any solid tumor with a *RET* gene alteration, as detected by an FDA-approved test. The approval of selpercatinib was based on the findings of a clinical trial in which nearly 50 percent of patients treated with the molecularly targeted therapeutic saw their tumors shrink.

Despite the significant progress in treatment, cancers remain one of the leading causes of death among US children and AYAs. With the rapid expansion of novel molecularly targeted therapeutics and immunotherapeutics, there is also an increasing need to monitor patients over time to better understand treatment-related long-term effects and morbidities. Additionally, there are disparities in clinical care experienced by children from racial and ethnic minority groups and other

von Hippel–Lindau syndrome is an inherited disorder **characterized by the formation of tumors** (e.g., kidney cancer and pancreatic cancer) **and benign cysts in different parts of the body**. Individuals with VHL develop tumors **most frequently during young adulthood**. Belzutifan (Welireg), the first drug for the treatment of VHL-associated tumors, was approved by FDA in August 2021.



W40

Travel times to the nearest pediatric oncologist were longest for the American Indian or Alaska Native population, residents of rural areas, and those living in areas with high levels of socioeconomic deprivation.

Source: (618).

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continued on page 128

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

Michael Methner

East Brunswick, New Jersey

A Message From Mike and Emily Methner, Michael's Parents

Dealing with intense, emergency situations is nothing new for Mike Methner, a 41-year-old police officer and his wife, Emily, a 39-year-old registered nurse. Yet, nothing could have prepared them for the journey that began one evening when Mike noticed something unusual about their son, Michael, who was just 2½ years old. His eyes were not quite right. There was a subtle but persistent at the time nystagmus, an involuntary eye movement. "I pointed it out to Emily, and she immediately got on the phone with the pediatrician."

> "Cancer doesn't have boundaries. It affects everyone irrespective of religion, political views, or orientation. We must have better treatments to help everybody, and that requires funding."
>
> – Mike and Emily Methner, Michael's parents

The pediatrician didn't think it was anything serious, but Mike and Emily noticed his vision issues appeared to be getting worse. Emily found a local eye doctor associated with Wills Eye Hospital in Philadelphia for a second opinion. Halfway through the examination, the doctor stopped and insisted an MRI was needed. "And that is when things started becoming very scary," Mike said.

The MRI revealed the worst—a brain tumor, known as glioma. The news hit like a freight train. Emily, who had spent her career caring for others, suddenly found herself on the other side, where she could do nothing but wait and hope. As a nurse, she knew all too well what the diagnosis meant. "It was shocking because we were expecting it to be a motor issue in his eyes. When we saw the size and location of the tumor and realized that it might kill him, we were completely devastated. They had to pay for our parking because we were crying hysterically as we were leaving the doctor's office," Emily said.

In those early days, the fear and uncertainty were overwhelming. While accustomed to facing emergencies at his job, Mike found himself unable to answer a simple question at FedEx about a document. It was the MRI results he was sending to Children's Hospital of Philadelphia. "The lady at FedEx says, 'What is the value of this document?' And I just started crying because it was priceless. And I didn't know what to tell her. And I just froze," Mike said.

Michael started treatment with chemotherapy. The drugs kept his tumor stable but there was no shrinkage. The side effects, however, were harsh, ranging from vomiting and hair loss to severe nerve pain. For 5 years, they endured the weekly infusions, hoping that the tumor would shrink or that a molecularly targeted treatment would become available. Unfortunately, Michael's tumor started to grow again. So, he was put on bevacizumab (Avastin), an antiangiogenic treatment. The tumor responded. However, the treatment severely impaired Michael's kidney function. "We had to go into the hospital because he was very close to having a stroke from his high blood pressure. And the moment you stop Avastin, the tumor just grows right back," Emily said.

Michael was next treated with a molecularly targeted therapeutic, trametinib, for about 2 years as part of a clinical trial. "That had a couple side effects that were rough. A lot of rashes, ingrown toenails, which had to be surgically taken care of. And unfortunately, the treatment wasn't working. It kept the tumor stable, but never shrank the tumor."

The strain on their family was immense. Lillian, Michael's sister, was too young to fully understand, but sensed the anxiety and the fear in her parents. She saw her brother getting sick, noticed the long trips to the hospital.

Finally, after years of struggle, a new molecularly targeted treatment, tovorafenib (Ojemda), became available. For the first time, they saw real progress. The tumor began to shrink, and while they knew the battle was far from over, it felt like they could finally breathe. "When we first started out his tumor was 51 millimeters by 45 millimeters and now it's cut in half, and we are beyond thankful," said Emily.

Today, Michael is a vibrant 10-year-old, full of life and energy. He loves playing video games, fencing, and reading, just like any other kid his age. His vision, while not perfect, has improved, and his parents are hopeful that he will lead a normal life. "Right now, Michael is doing wonderfully. He is just a regular kid. You wouldn't be able to pick him out from a group of kids on the sidewalk," Emily said.

Michael's experience with cancer has made his parents passionate advocates for medical research. "Cancer doesn't have boundaries. It affects everyone irrespective of religion, political views, or orientation," Mike said. "We must have better treatments to help everybody, and that requires funding." Their hope is that increased funding for cancer research will lead to new clinical breakthroughs, improve outcomes, and eliminate toxicities. "If we can find better medications that aren't as toxic to the kids and have benefits, you can't put a price tag on that."

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

Parker Shaw

Lakeside, California

A Message From Dave and Crystal Shaw, Parker's Parents

Parker was a typical 6-year-old boy with boundless energy, whether he was scootering down the street, riding his bike, or swinging from tree branches. One day in March 2013, at a birthday party, Parker and his friends were swinging on the branch of a tree when the branch gave way. He fell, hitting the back of his left hip on a stump. Although he complained about the bruise, Crystal, who is a nurse, didn't think much of it and Parker continued to scooter around and play as usual. But over the next 2 weeks, something began to change.

Parker started complaining more frequently about pain in his hip, sometimes pointing to his abdomen instead. Despite the pain, Parker remained active. Crystal, concerned but not overly alarmed, chalked it up to growing pains, something she had heard other moms talk about.

It wasn't until after spring break, when Parker's teacher mentioned that he wasn't acting like himself, that Crystal decided to take him to the doctor. She thought maybe Parker had an infection in his hip bone. The doctor agreed with her and sent them to the hospital.

During the trip to the hospital, Parker had a high fever and was unusually quiet. They completed lab work and an X-ray, then returned home. That night, Crystal received a call from the pediatrician. While the X-ray was normal, Parker's laboratory results were not. The markers of inflammation or infection were 10 times the normal levels. The doctor recommended a CT scan and said if Parker's condition worsened to go to the hospital to speed up the scan.

"More investment in cutting-edge, less toxic treatments is crucial—not just for Parker, but for the future of all children battling cancer."

– Dave and Crystal Shaw, Parker's parents

The next morning, Parker woke up screaming in pain, unable to walk. Crystal rushed him to the ER, where Parker was given an MRI to limit his radiation exposure.

After the scan, the mood of the hospital staff shifted. Crystal was approached by a visibly upset doctor, joined by a social worker, who revealed a mass was found on Parker's left kidney. "And my nurse brain just started jogging all the things; what could this be?" The doctor suspected Parker had neuroblastoma.

In the days that followed, Crystal and Dave were engulfed in a whirlwind of emotions—anger, confusion, fear. But they had to be strong, not just for Parker, but for their whole family.

Tests confirmed that Parker's cancer had spread to 87 percent of his bone marrow, with metastases throughout his body. The prognosis was poor. Crystal and Dave researched neuroblastoma, joined support groups, and consulted with other parents. Eventually, they made the difficult decision to move their family from San Diego to New York, where a specialized team of doctors at the top of their field in neuroblastoma could provide the best possible care.

Parker underwent several rounds of chemotherapy followed by surgery to remove the tumor. The surgery lasted over 10 hours and the road to recovery was long and painful. Parker was resilient. He next underwent additional chemotherapy followed by an experimental immunotherapy known as natural killer cell therapy, along with an investigational treatment, naxitamab.

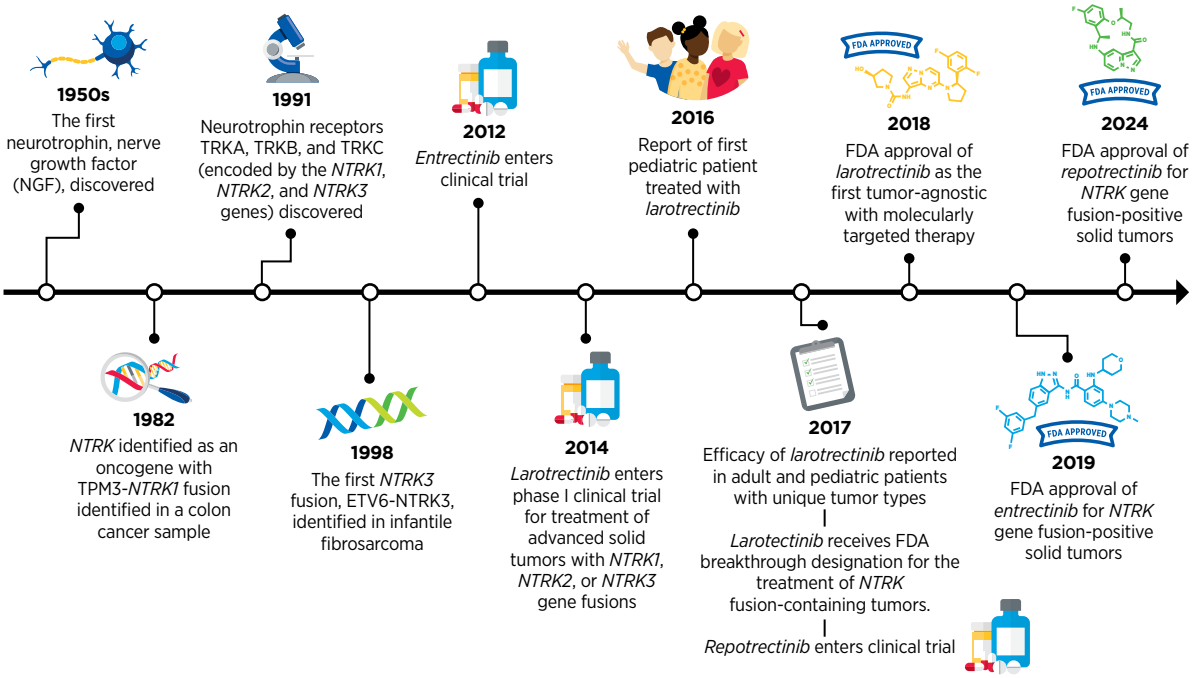
After 10 rounds of immunotherapy followed by radiation, Parker's condition finally began to improve. "On January 10, 2014, for the first time, Parker reached NED status, which means no evidence of disease. He was cancer free," Crystal said. Encouraged by Parker's response to the investigational treatment, Dave and Crystal pursued another clinical trial of eflornithine to reduce the risk of relapse.

Eflornithine has been effective for Parker. Now 17, Parker is thriving. Their experience with cancer led Dave and Crystal to start a foundation called Team Parker for Life. "We raise money for clinical research and to date have raised $1.875 million. We also help kids and their families across the United States so they do not have to worry about paying the next house payment or for their car and gas," Dave said.

Crystal and Dave underscore the importance of funding cancer research, especially for childhood cancers, which receive only a small fraction of the overall budget. "More investment in cutting-edge, less toxic treatments is crucial—not just for Parker, but for the future of all children battling cancer," they said.

★ FIGURE 20

Research Milestones on the Road to Developing TRK-targeted Therapeutics



Decades of basic, translational, and clinical research paved the way for the landmark approval of larotrectinib, followed by entrectinib and repotrectinib, starting with the seminal identification of the first neurotrophin, nerve growth factor, in the 1950s. Other basic research milestones on the way to FDA approval are the identification of the neurotrophin receptor proteins, TRKA, TRKB, and TRKC, and the genes that encode these proteins, *NTRK1*, *NTRK2*, and *NTRK3*, and the discovery that *NTRK* fusion genes and proteins fuel the growth of a wide array of cancer types that occur in adults and children. Together, this body of research led to the development of the three TRK-targeted therapeutics, which target TRKA, TRKB, and TRKC, and their testing in basket clinical trials involving patients who have cancers driven by an *NTRK* gene fusion.

medically underserved populations. Continued progress against childhood and AYA cancers necessitates increasing collaboration among all stakeholders in medical research so that the new wave of innovation in cancer science and technologies, coupled with advances in regulatory policies and legislation (see **Accelerating Progress Against Childhood Cancer**, p. 163), can drive new breakthroughs that benefit all patients.

Supporting Cancer Patients and Survivors

IN THIS SECTION, YOU WILL LEARN:

- As of 2022, there were an estimated 18.1 million people living with a history of a cancer diagnosis.
- Cancer patients and survivors face a multitude of physical, emotional, and financial challenges because of their cancer and treatment.
- Childhood, adolescent, and young adult cancer survivors face unique challenges including long-term side effects from cancer and its treatments, difficulty finding work, lower levels of educational attainment, and psychosocial issues.
- Eating a healthy diet, reducing alcohol consumption and tobacco use, and exercising can improve the survivorship experience and outcomes.
- Caregivers of patients with cancer can face the same negative health and social consequences as the family members and loved ones they are caring 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 2022, the most recent year for which such data are available, there were 18.1 million people living with a history of a cancer diagnosis, which equates to about 5 percent of the US population (9). This is a significant improvement from 50 years ago when cancer survivors constituted only 1.4 percent of the US population. The number of survivors is expected to grow to 26 million by 2040 (9).

As more people are living longer and fuller lives after a cancer diagnosis, greater attention is needed to understand survivorship experiences. These experiences include the physical, psychosocial, and economic adversities caused by a cancer diagnosis. Cancer survivors are also at a risk for late effects or secondary health problems due to their cancer treatments and therefore require long-term follow-up care, which includes screening for these late effects. Survivorship care should include secondary cancer prevention counseling and assessment for short-term and late effects, including the increased risk of co-morbidities, recurrence, and development of secondary cancers.

A diagnosis of cancer also impacts friends, family members, and caregivers, who are often the main support network for the survivor. This necessitates widening the focus of research, support, and care beyond the cancer patient and survivor to include individuals who make up the support structure.

The following sections highlight the challenges faced by cancer survivors and their support network, strategies to improve quality of life, and approaches that have been shown to deliver care most effectively.

Challenges Faced by Survivors

Cancer survivors often face physical, psychosocial, and financial challenges throughout their survivorship journey. Collectively these challenges contribute to the overall health-related quality of life (HRQOL) experienced by cancer survivors. Overall, HRQOL is lower among cancer survivors compared to those who have never had a diagnosis of cancer. Findings from a recent study show that cancer survivors with the lowest HRQOL were more likely to be unemployed, lacked social support, and were less prepared for survivorship. They also ate a less healthy diet and had more comorbidities, and were more concerned about the risk of cancer recurrence or secondary cancers (619). Cancer survivors also experience higher functional limitations, such as the inability to sit for extended periods of time or participate in social activities. The proportion of survivors who experience these limitations have doubled over the past two decades, with the highest prevalence among survivors of pancreatic cancer and lung cancer (620).

While research over the years has highlighted many of these challenges, implementation of groundbreaking new treatments such as immunotherapy and cell-based therapies can also present unique short- and long-term challenges. A greater understanding of these challenges and ways to address them is urgently required to support cancer survivors.

Physical Challenges

Survivors can experience a wide range of short- and long-term symptoms caused by cancer or its treatments. Short-term effects include hair loss, pain, nausea, vomiting, and loss of smell and appetite with varying severity of symptoms depending on the person, cancer type, and treatment. As cancer survivors are living longer, 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 40**, p. 131).

Of primary concern for cancer survivors is the fear of cancer recurrence or the diagnosis of new cancers (621,622). Rates of cancer recurrence or diagnosis of new cancers is dependent on many factors, including type and stage of cancer, the type of treatment received, and physical and socioeconomic factors. The chance of recurrence is higher for people treated for childhood cancers (see **Cancer Survivorship in Childhood and AYAs**, p. 133) and adult survivors of Hodgkin lymphoma, glioblastoma, certain types of soft tissue sarcoma, bladder and pancreas cancer, and cancers caused by tobacco use (623). Primary cancers that are caught early have a lower risk of recurrence.

Cachexia is the loss of body weight and muscle mass, and the weakness that may occur in patients with cancer or other chronic diseases. Cachexia is estimated to occur in about 50 percent to 80 percent of patients with cancer and causes about 20 percent of cancer-related deaths (624). The development of cachexia results from multiple factors, including reduced nutrient intake while on active treatment, increased energy demand from cancer cells, reduced physical mobility of cancer patients, as well as inflammation associated with cancer and cancer treatments. Recent evidence has shown that patients with cancer who developed cachexia had higher rates of depression (30.2 percent), anxiety (18.6 percent), severe depression (6.7 percent), and severe anxiety (8.4 percent) compared to those who did not develop cachexia. Cancer survivors who developed cachexia also had lower overall HRQOL (625). Understanding the biological underpinnings of cancer-related cachexia as well as developing novel therapeutic approaches that prevent cachexia is critical to reduce the loss of muscle mass in patients with cancer and improve their overall survival.

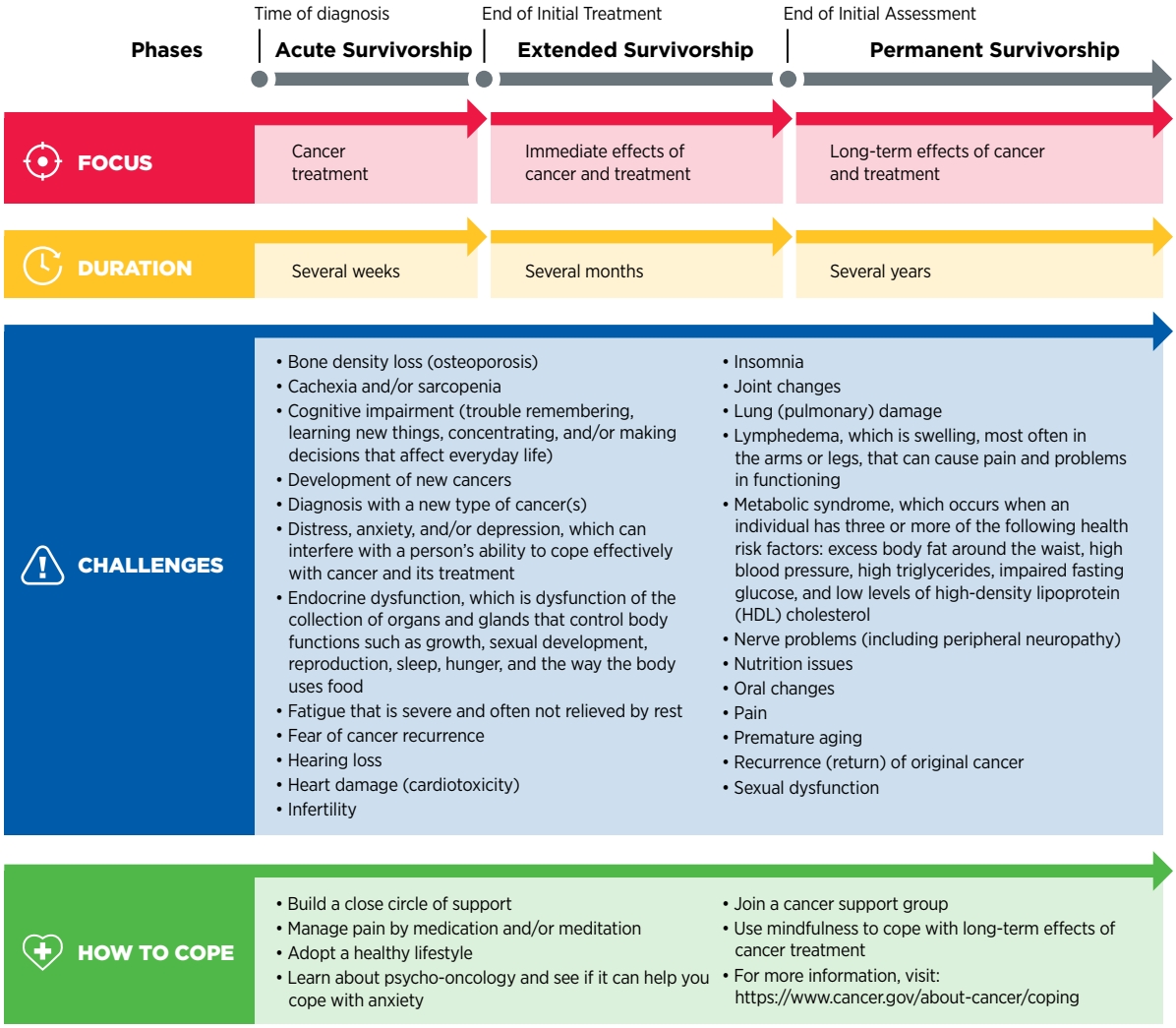
Chemotherapy-related cognitive impairment, often termed "chemo brain," describes thinking and memory problems before, during, and after cancer treatment and has been reported by many cancer survivors (626). Cognitive impairment is very common among survivors of childhood cancer (see **Cancer Survivorship in Childhood and AYAs**, p. 133). One meta-analysis estimated that chemotherapy-induced cognitive impairment was as high as 65 percent among breast cancer survivors (627). Cognitive impairment among survivors also reduces their HRQOL (627). It is critical that behavioral and therapeutic interventions be in place to reduce the effect of cognitive impairment on survivors.

Emerging evidence shows that cancer survivors have increased incidence of age-related diseases and faster functional decline compared to individuals who do not have a history of cancer (628-630). This is partly due to changes at the molecular level as a result of certain types of cancer therapies. For instance, researchers who measured age-associated methylation marks on the DNA of women who had breast cancer and were treated with radiation found methylation patterns similar to those individuals who did

SIDEBAR 40

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.

not have a history of cancer but were much older (631). Some examples of age-related diseases associated with cancer treatment include clinical hypertension, coronary artery disease, heart failure, and atrial fibrillation, arising from cardiotoxicity induced by certain types of anticancer therapeutics. In older adult cancer survivors, anti-hormonal treatments, such as tamoxifen, are associated with premature cognitive decline, while androgen deprivation therapy, primarily used to treat prostate cancer, is associated with increased risk of Alzheimer's disease (632).

Psychosocial Challenges

A diagnosis of cancer can pose serious challenges to a person's psychosocial state and involves both psychological and social adversities. These challenges include uncertainty about the future and the possibility of cancer recurrence, isolation and lack of understanding by peers who do not have a history of a cancer diagnosis, returning to work, quality of care, and potential lack of support and coping strategies (633).

According to a recent study in women with breast cancer, psychosocial well-being initially declined after diagnosis; however, their emotional functioning improved over time, with the greatest improvements among women who received breast reconstruction (634). Side effects from cancer can also contribute to psychosocial challenges. For example, survivors of gynecologic cancers with lymphedema symptoms, i.e., swelling, numbness, and/or tingling near sites of surgery, had lower quality of life, greater psychosocial distress, and negative views of body image, compared to those without lymphedema symptoms (635).

Financial Challenges

Financial toxicity refers to the financial hardship associated with cancer treatment and management. It is well established that cancer patients and survivors are at higher risk of experiencing financial difficulties compared to individuals without a history of cancer. One report estimates that more than 40 percent of cancer patients can spend their entire life savings within the first 2 years of cancer treatment (636). The reported total out-of-pocket expenses for prostate cancer treatment ranged from $1700 to $3000. For many, this unexpected expense can lead to financial hardships and distress (637).

Importantly, the cost of cancer does not end after the completion of treatment. Post-treatment costs include managing the late and long-term effects of cancer and its treatments, mental health care, and treatment of secondary cancers.

Evidence indicates that cancer survivors who experience financial toxicity and subsequently have difficulty paying for prescriptions, mental health care, and other health services, and/or who delay medical care due to cost, are also at greater risk of mortality, regardless of insurance status (639). To mitigate these financial challenges, survivors often utilize coping behaviors. These include medication underuse or skipping medication doses; cutting back on spending, including for essential items, such as food; and missing payments, including for rent or a mortgage (640).

Exacerbating financial toxicity among survivors is the inability to continue working or, after the conclusion of treatment, returning to a previous job. The type of work that a person does prior to their cancer diagnosis also impacts their ability to retain a job or return after treatment concludes. In a study of rural women cancer survivors, those who had less secure jobs, including temporary, part-time, or non-traditional jobs, were less likely to return to work compared to those with secure employment (641). This is concerning because research shows that being employed improved HRQOL among cancer survivors (642). To ensure job security among cancer survivors during and after treatment, employers should create policies, such as modifying the demands of the work environment, in consultation with employees and their health care providers to accomodate the unique needs and challenges faced by cancer survivors.

Unique Challenges Faced by Older Adults

Older adults are defined as those age 65 and over, representing 64 percent of cancer survivors in the United States. This population is also the fastest growing and is projected to increase to 73 percent of cancer survivors by 2040 (643).

Older cancer patients are susceptible to being malnourished, which can exacerbate muscle wasting (sarcopenia) and weight loss due to cancer (cachexia). One study found that among older adults with cancer, 60 percent were malnourished, 53.3 percent had sarcopenia, and 56.7 percent had cachexia, with 30 percent of adult cancer survivors having all three conditions together (644). These side effects often stem from decreased nutrient intake. The use of certain drugs that improve appetite has been shown to help increase nutritional intake; however,

Worldwide, **financial toxicity for patients with breast cancer was 78.8 percent in low- and middle-income countries** and 35.3 percent in high-income countries.

Source: (638).

W42

these can also lead to gastrointestinal and cardiovascular complications (645). Other strategies have been explored, such as the use of probiotics and low-dose olanzapine, which have shown some promise in boosting survivors' appetites and reducing weight loss among cancer patients on active treatment (645-647).

Although the evidence is still scarce, older adults are also susceptible to adverse mental health events. Of particular concern among this population is loneliness, with some estimates showing that up to 50 percent of older adults experience loneliness (648). Furthermore, other adverse mental health events, including depression and anxiety, are exacerbated by loneliness (648). This is concerning because some evidence suggests loneliness among cancer survivors over the age of 50 reduces HRQOL and nearly doubles the risk of mortality (649). Interventions to reduce loneliness and improve HRQOL among this population include social support, telehealth strategies, and other types of counseling (650).

As older cancer survivors often have other pre-existing chronic conditions that require regular medication, adding a cancer therapeutic after a diagnosis of cancer can lead to "polypharmacy," which has been associated with numerous adverse outcomes. Polypharmacy can lead to drug-drug interactions, faster functional decline, falls, hospitalizations, and mortality in older adults (651-657). The issue is exacerbated when physicians prescribe more medications to counteract the symptoms of polypharmacy. One study of older adult cancer survivors found that 61.3 percent of these individuals were being given five or more medications, with 14.5 percent who were being given 10 or more (658). Of those who were considered to have polypharmacy, 67.1 percent experienced at least one adverse reaction between their cancer drug and other medications they were taking (658).

Older adult cancer survivors are also susceptible to financial challenges. While most older adults have insurance, the financial burden of cancer can continue long after conclusion of treatment (659,660). After diagnosis, older adults that received a diagnosis of cancer incurred more consumer debt compared to those without a diagnosis of cancer (34.5 vs. 29.9 percent) that persisted 2 years after (659).

★ SPOTLIGHT

Cancer Survivorship in Childhood and AYAs

Childhood and adolescent and young adult (AYA) cancer survivors face unique challenges compared to their peers who have never had a diagnosis of cancer. These challenges include long and late-term side effects from cancer and its treatment, financial toxicity, difficulty finding work, lower levels of educational attainment, psychosocial issues, and others. Because of the unique challenges faced by this population, researchers and care providers must pay special attention to ensure the needs of this population are adequately addressed across the spectrum of cancer care.

Challenges Faced by Childhood and AYA Cancer Survivors

In the United States in 2024, an estimated 9,620 new cases of cancer will be diagnosed among children. Thanks to major treatment advances, 85 percent of children are expected to live 5 years or more after a cancer diagnosis. This is a marked improvement compared to the mid-1970s, when only 42 percent of children lived beyond 5 years after a cancer diagnosis (661). Because childhood cancer survivors are diagnosed at a young age, they live longer postdiagnosis than an adult who has been diagnosed with cancer later in life.

Due to this longer lifespan, childhood cancer survivors are more susceptible to late-stage side effects for a variety of reasons, including the type and stage of cancer at the time of diagnosis, the type and dose of treatment, and the age and general health of the patient at the time of treatment. Reports indicate that 60 to 90 percent of childhood survivors develop one or more chronic health conditions following their cancer diagnosis (662,663).

Childhood cancer survivors are at an increased risk of developing a new cancer due to late effects of cancer treatment and/or inherited genetic factors (657). Additionally, children with a cancer diagnosis who receive chemotherapeutics are at an increased risk of developing hearing loss, also called ototoxicity. One study found that 75 percent of children under 5 and 48 percent of children over 5 who were treated with cisplatin had hearing loss related to their treatment (664). In September 2022, the US Food and Drug Administration (FDA) approved sodium thiosulfate to reduce the risk of hearing loss associated with the chemotherapeutic cisplatin in childhood patients with cancer 1 month and older. Sodium thiosulfate reduced the risk of cisplatin-associated hearing loss by almost 60 percent compared

AS A RESULT OF CANCER TREATMENTS, **SURVIVORS OF CHILDHOOD CANCERS MEASURED 16 YEARS OLDER, BIOLOGICALLY.**

Source: (669).

W43

MORE LIKELY

A new primary cancer or secondary cancer diagnosis is twice and 1.3 times as likely in male and female **AYA cancer survivors**, respectively, compared to those without a history of cancer.

Source: (675).

W44

to those who did not receive the drug (665). Long-term survivors of childhood cancer are also at an elevated risk for late-onset cognitive impairment, which are declines in memory, thinking, and psychomotor tasks. In one study of childhood cancer survivors, researchers found that memory impairment was as much as 34 percent higher in survivors who were treated for cancers of the central nervous system, compared to siblings who did not undergo cancer treatment (666).

Premature aging, which refers to the early onset of aging-related health issues, is common among childhood cancer survivors (667). These include chronic conditions such as cardiovascular disease, endocrinopathies, and other cancers. According to one study, daily functional limitations, psychosocial symptoms, and health conditions of a 30-year-old survivor of a childhood cancer are similar to those of a 63-year-old healthy individual (668).

Adolescent and young adult (AYA) cancer survivors are those diagnosed between the ages of 15 and 39. Based on estimates of new cancer cases in 2024, 4.2 percent of all new cases will be in AYA and 85.9 percent of AYAs diagnosed with cancer will live 5 years or more after their diagnosis (3). This population group faces unique personal, social, and emotional challenges as highlighted in the personal story of **Lourdes Monje** (see p. 137).

Many AYA survivors experience long-term side effects and are at a two- to three-fold higher risk of premature ovarian failure, chronic liver disease, renal failure, and cardiovascular disease, compared to those with no diagnosis of cancer (670). A recent study reported that 40 percent of AYA survivors had more than one chronic condition (e.g., cardiomyopathy, hearing loss, stroke, diabetes) 10 years after their cancer diagnosis, compared to only 20 percent of those who did not have cancer (670).

Similar to childhood cancer survivors, AYA cancer survivors also have a higher risk of secondary cancer,

★ SIDEBAR 41

Fertility Preservation After a Diagnosis of Cancer

One of the adverse consequences of cancer treatments is infertility, or the inability to conceive a child. This may result from surgery on reproductive organs or effects of cancer medications on reproductive cells, and can affect both male and female patients. Thus, those diagnosed with cancer should consider discussing with their health care providers whether infertility is a risk for them and, if so, if 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. Furthermore, as of July 2024, 18 states have mandates, and two have active legislation, requiring insurance coverage of fertility preservation for patients facing infertility due to treatments such as anticancer therapies (677). This is an increase from July 2022, when only 12 states had such mandates.

which is partly due to premature aging (671-673). AYA cancer survivors are twice as likely to die from the development of a new primary cancer as those who have never had a diagnosis of cancer (674).

Between 44 percent and 86 percent of AYA survivors have concerns regarding how treatments for cancer, including surgery, radiotherapy, and cytotoxic chemotherapy, may lead to infertility, which is the inability to conceive a child (676). The possibility of impaired reproductive abilities may lead some patients to store reproductive material through the process of fertility preservation (see **Sidebar 41**, p. 134). Participation in fertility preservation and the type of preservation should be decided by individuals after discussions with their health care providers.

Intrathecal therapies in children, for instance in children treated with methotrexate for medulloblastoma, can lead to impairments in cognition, executive functioning and short-term memory (678). AYA survivors also experience cancer-related cognitive impairment, which is more common in survivors of central nervous system cancers, Hodgkin lymphoma, and testicular and breast cancers (679). Although research in cancer-related cognitive impairment among AYA is lacking, it has been estimated that 22 percent of AYA cancer survivors experience problems with memory (680).

The psychosocial impact of a cancer diagnosis on a child can be traumatizing and have a lasting effect on the mental health of childhood survivors of cancer. Research on the social aspects of cancer in children have shown that they harbor negative perceptions of their appearance, leading to problems with academics, social interactions, and psychological well-being, resulting in low self-esteem and depression, all of which can be exacerbated by bullying and ridicule from peers (681-683).

It is estimated that AYA cancer survivors experience:

32% psychological distress

29% anxiety

24% depression

Source: (688).

W45

Among adult survivors of childhood cancers:

29.9% report being **sent to debt collection** for unpaid bills.

26.8% said they **didn't have enough money** to buy nutritious meals.

20.7% had **problems paying** medical bills.

14.1% had to **forgo medical care** because they could not afford it.

Source: (694).

W46

The quality of mental health among survivors of childhood cancers is also concerning. When compared to their healthy siblings, young adult survivors of childhood cancers reported increased loneliness that subsequently increased anxiety, depression, and the likelihood of smoking. Long-term follow-up with these patients found higher levels of suicidal thoughts, as well as heavy/risky alcohol consumption (684). This population is also more susceptible to major mental health illnesses, including autism, attention-deficit disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and posttraumatic stress disorder, with the greatest number of mental health illnesses experienced by survivors of brain and blood cancers (685).

Similar to survivors of childhood cancers, AYA cancer survivors also have worse mental health outcomes compared to those without a diagnosis of cancer. AYA cancer survivors had an 80 percent increased risk of hospitalizations for mental health illnesses and were 4.5 times more likely to purchase antidepressants compared to their siblings (686,687).

Financial toxicity is prevalent among survivors of childhood cancer (689). The reasons for financial toxicity among this population are multifaceted and include continuing medical expenses associated with long- and late-term side effects; difficulty finding and retaining employment because of cancer- and treatment-related disabilities; and lower-paying jobs, partially as a result of lower educational attainment (690-693).

Also concerning is the decline in employment among childhood cancer survivors over time, with full- or part-time employment declining by 6.5 percent and 8 percent

continued on page 138

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

Lourdes Monje

Philadelphia, Pennsylvania

Lourdes Monje had always been mindful about their health, regularly performing self-checks as advised. One morning, in October 2020, something felt different—a mass in their chest that hadn't been there before. The unexpected discovery changed everything.

Lourdes was 25 at the time and in the process of moving from New York with the goal of launching a professional career in Philadelphia. They didn't have a primary care provider, which coupled with the challenges brought on by the ongoing COVID-19 pandemic, added to the anxiety of the situation. However, Lourdes was able to get an appointment with their sister's primary care physician.

> "There are a lot of really specific challenges as a young adult diagnosed with cancer, specifically metastatic breast cancer—like the prospect of having children, the prospect of having a career."

The doctor recommended an ultrasound. "When the ultrasound technician saw the imaging, they called in another doctor. I knew things were a little bit iffy. They recommended that I go in for a biopsy and that is where the fear started." The next day, the doctor called with the official diagnosis of breast cancer. "I felt my world stop. All my plans had to go out the window. It was just about getting this taken care of," Lourdes said.

Unsure of what to do next, Lourdes turned to their primary care doctor for guidance on how to prepare for their visit with the oncologist. "I talked to my primary care doctor because I had no idea how to talk to an oncologist or what I was supposed to be asking." After speaking with a surgical oncologist, Lourdes underwent a series of scans over the following weeks—MRIs, CTs, and finally a PET scan. Each scan provided additional information, and a follow-up biopsy of the lymph nodes confirmed stage IV breast cancer.

While the path to their diagnosis was complicated due to the pandemic, Lourdes was grateful to have been taken seriously from the start. They received the diagnosis of stage IV breast cancer in January 2021. The idea of cancer was terrifying, something Lourdes had never anticipated so young. They were devastated.

In their mind, the words "stage IV" were synonymous with death. However, their oncologist explained that while the cancer was technically stage IV, it was still treatable. Lourdes began treatment with hormone suppression and the molecularly targeted therapeutic, ribociclib (Kisqali). The treatment worked for 6 months before a switch was made to another molecularly targeted drug, palbociclib (Ibrance), which they remained on for over 2 years.

During this period, Lourdes also underwent a mastectomy and radiation therapy. A follow-up scan, however, revealed nodules in a lung. This news was unexpected and crushing after a period of stability. Their doctor recommended a clinical trial as the best chance for finding the more effective treatment. Fortunately, Lourdes qualified for a trial at the Sidney Kimmel Comprehensive Cancer Center at Jefferson Health and has been receiving an investigational therapeutic for several months now.

The clinical trial has come with its own set of challenges, including managing some anticipated side effects, but Lourdes remains hopeful. "It was a little bit difficult. There was a moment of not knowing if I was gonna have to just get off the drug altogether, but things have settled down now." Despite the fears and uncertainties, they said participating in the trial feels like an opportunity not just for personal healing, but also for contributing to future advancements in cancer medicine. "The way I've been approaching this trial is knowing that it's not just for me, it's for other people who will come after me. Because I know that the two medications that I had access to beforehand that are relatively new are because of people like me who went through clinical trials," they said.

Throughout their journey, Lourdes has also navigated the complexities of gender identity. During the process, they began to understand more about being nonbinary. Decisions about breast reconstruction brought up questions about personal comfort with gender expression. Lourdes's surgeon was supportive, and the conversations were respectful and affirming. While Lourdes hasn't faced discrimination, there's always a sense of vulnerability when sharing this part of identity with health care providers. "Even though I haven't been treated badly, just the fact that there's a part of me that is hesitant to be my full self is an issue," Lourdes said. These experiences underscore the importance of small but significant changes in the health care system, like asking for preferred pronouns or including space for preferred names on forms.

Living with stage IV cancer presents many challenges. "There are a lot of really specific challenges as a young adult diagnosed with cancer, specifically metastatic breast cancer—like the prospect of having children, the prospect of having a career." Watching friends progress in their careers, start committed relationships, and start families was difficult, knowing that personal plans had to be put on hold. For a long time, it felt like managing the diagnosis was Lourdes's full-time job. But being part of the clinical trial has brought new hope. The side effects have been manageable, allowing Lourdes to continue working and spending time with their family, friends, and their sweet dog. "I feel like I'm having as normal of a life as I can and creating the memories that I've wanted to, that are so important to me."

among female and male childhood cancer survivors, respectively, over 10 years after diagnosis (691).

Financial toxicity among AYA cancer survivors is also higher compared to those with no diagnosis of cancer (695). One study reported that the costs associated with a diagnosis of cancer are substantial, reaching an average of $259,324 per person over their lifetime (64). One reason is that a cancer diagnosis often affects these individuals when they are just beginning higher levels of education or starting careers, potentially impacting productivity and well-being (64).

In one study, researchers examined how a diagnosis of cancer as an AYA led to hardships into adulthood across three domains, which were material (e.g., paying bills, medical care), psychological (e.g., distress), and behavioral (forgoing medical care). Those adults with a diagnosis of cancer as an AYA were 38 percent more likely to report hardship across all three domains compared to those without a diagnosis of cancer as AYA (696).

As childhood and AYA survivors of cancer are living longer, thanks to improved treatments, greater attention should be given to follow-up care and continued surveillance strategies should be implemented for cancer recurrence or the development of new cancers. A particular concern is that medical records may not be transferred when childhood cancer survivors grow up and transition to adult health care settings (697). The Childhood Cancer STAR Reauthorization Act was signed into law in January 2023, reauthorizing the program for an additional 5 years at its fully authorized level of $30 million. This legislation hopes to not only improve treatments for childhood and AYA cancer survivors, but also improve cancer surveillance, and enhance resources for survivors and families (see **Accelerating Progress Against Childhood Cancer**, p. 163) (698).

Health care systems, policymakers, and other stakeholders must recognize the adverse effects of financial toxicity among AYA cancer survivors to design interventional strategies necessary to address the underlying causes.

Promoting Health in Childhood and AYA Cancer Survivors

A healthy diet, maintaining a healthy weight, and regular exercise are important for any child or AYA to stay healthy and curtail obesity, while AYA populations should abstain from smoking cigarettes and tobacco, as well as limit alcohol consumption. For children and AYA individuals who receive a cancer diagnosis, adhering to a healthy diet and exercise can be a challenge. A key focus for these patients should be not only maintaining a healthy weight and participating in regular physical activity but also escalating these goals for continued growth and development. One of the side effects that accompany cancer is a lack of appetite, which can lead to unintended weight loss. Studies show that higher treatment intensities among children with cancer increase the likelihood of weight loss, especially in younger children (699). Studies have shown that a registered dietitian or nutritionist, who can intervene before, during, and after treatment, can help children stay on a healthy diet and maintain weight (700).

Eating a healthy diet, particularly one based on fruits, vegetables, and whole grains and low in processed foods and red meats, can reduce long-term side effects and mortality from cancer. In long-term studies of survivors of childhood cancers, individuals who consumed dark green vegetables and nuts/seeds saw a reduction in premature aging (701). Strategies that increase consumption of healthy foods are paramount to reducing the development of chronic conditions, obesity, and adverse side effects among AYA cancer survivors.

Exercise can help survivors of childhood and AYA cancer minimize adverse long-term outcomes, such as chronic health conditions, and treatment-related side effects (702,703). Although data are limited in this area, interventions that are digitally based worked best for these individuals (704). Among AYA cancer survivors, participating in moderate- to vigorous-intensity physical activity led to a 40 percent reduction in cardiovascular disease, a common chronic condition among this population (705). Designing interventions that help children and AYA individuals with a history of a cancer diagnosis maintain the recommended physical activity guidelines is necessary to reduce the adverse effects of cancer in these populations (see **Sidebar 11**, p. 51).

Smoking among cancer survivors is associated with poor outcomes and greater treatment-related complications, higher risk of secondary cancers, lower HRQOL, and greater mortality (706,707). It is therefore concerning that an estimated 20 percent to 22 percent of survivors of pediatric cancer smoke (708,709) and 33 percent of AYA cancer survivors smoke (710). Evidence regarding interventional strategies that are directed toward childhood or AYA cancer survivors is insufficient. Cessation strategies that are tailored to the unique needs of this population are necessary to reduce the burden of smoking among this population.

Mental health care among childhood and AYA cancer patients and survivors requires collaboration among health professionals, school administrators, parents,

★ SIDEBAR 42

Support for Childhood and AYA Cancer Patients and Survivors

The diagnosis of cancer for children and AYA is a life-changing event and presents many unique challenges, especially concerning mental health. Discussing both the physical and emotional aspects of a diagnosis of cancer and the subsequent treatments is paramount to helping mitigate the negative aspects.

Physical support:

- Continuing to **maintain relationships** with friends.
- Continuing to **participate in** the **activities and hobbies** that are important and bring joy.
- **Maintaining a journal** to help manage thoughts and experiences.
- **Reaching out** to the cancer advocacy community to help connect with other survivors and patients.
- **Participating in physical activities** to help improve physical and mental health.

Emotional support:

- **Acknowledging and embracing emotions**, such as occasionally feeling sad, but being wary of long-term episodes of negative emotions.
- **Seeking help** from mental health experts to address any long-term concerns and improve mental health.
- **Participating in** age-specific **support groups** and programs.
- **Utilizing mind-body practices** to relax.
- **Finding comfort in praying, meditating, and reaching out** to spiritual leaders, all of which can help deal with the numerous challenges brought on by a diagnosis of cancer.

Educational support:

- **Accommodating individuals** with a diagnosis or history of cancer in school through the Rehabilitation Act of 1973, the Individuals with Disabilities Act (IDEA), and Americans with Disabilities Act.
- **Using a computer or voice recorder** for students with handwriting challenges.
- **Using a calculator, graph paper, and math formula list** to help with math challenges.
- **Accommodating challenges with attention** such as sitting in the front of the classroom, extended time on tests, and taking tests in separate rooms.
- **Providing extra travel time between classes,** adaptive physical education activities, and physically accessible facilities.

Source: (711).

and survivors. Because cancer is rare in children, there is a dearth of widespread policies and procedures to effectively deal with a diagnosis of cancer. However, a few strategies can be employed to help this population find the support they need to help deal with a cancer diagnosis (see **Sidebar 42**, p. 139).

The challenges in those aged 40 to 49 are of increasing concern because cases of early-onset cancers in this age group are rising compared to early-onset cancers in younger ages. Like survivors of other ages, this population faces similar challenges including reduced quality of life, sexual dysfunction, negative body image, financial and career impacts, and social and family impacts (712).

Improving Health-related Quality of Life and Outcomes

Healthy behaviors, such as physical activity, a healthy diet, reduced alcohol consumption, and smoking cessation, can

Cancer patients who participated in live, online classes for **yoga, tai chi, meditation, and dance therapy reduced the occurrence** of common side effects of cancer treatment, including **fatigue, anxiety, and depression**.

Source: (720).

W47

significantly improve both health outcomes and HRQOL for cancer survivors. In fact, it is increasingly appreciated that adopting healthy behaviors after a diagnosis of cancer, but prior to beginning cancer treatment, can significantly improve outcomes for patients (713,714). A patient who is healthy at the start of treatment can undergo treatment with higher doses of drug, is less susceptible to certain side effects, and has an immune system that is primed to fight cancer better (715).

Participating in Physical Activity

Physical activity has been shown to increase survival and lower recurrence of cancers (716,717). Research shows that cancer patients and survivors who participated in the recommended physical activity guidelines (see **Sidebar 11**, p. 51) had lowered rates of mortality compared to those who did not participate in physical activities (718). Emerging evidence suggests that physical activity can improve the immune system's ability to detect and remove cancer cells (719). This can be beneficial to individuals who are predisposed to cancer, such as patients with Lynch syndrome, who develop certain types of cancers, including colorectal cancer, more frequently than those without Lynch syndrome (719). With a more active and effective immune system, pre-cancerous cells that are more common in patients with Lynch syndrome can be intercepted before they develop into cancer.

Other types of interventions such as low-impact, meditative movement can improve outcomes among cancer patients and survivors (721,722). Mindfulness interventions can also reduce the severity of cognitive impairment among cancer survivors (723-725). Mind-body interventions, for example yoga, which are often low impact, can also help cancer patients and survivors transition into more physically strenuous exercises (721).

Eating a Healthy Diet and Maintaining a Healthy Weight

Consuming a healthy diet that incorporates whole grains, fruits, and vegetables can increase survival from cancer and reduce the risk of cancer recurrence (726). In fact, it has been reported that eating a healthy diet can lower overall mortality and cancer-specific mortality by 20 percent and 14 percent, respectively, in an analysis of cancer survivors globally (727).

Plant-based diets reduce mortality among cancer patients and lead to weight loss and improved cardiovascular health (728,729). Certain diets that emphasize plants and healthy fats, such as the Mediterranean diet, have been associated with reduced overall mortality in cancer patients and survivors (730-733).

Conversely, consumption of unhealthy foods such as ultra-processed products, red meat, and sugar-sweetened beverages increased fatigue and chemotherapy-induced peripheral neuropathy while reducing HRQOL among cancer survivors (734,735).

Emphasizing a healthier diet can help improve HRQOL, reduce side effects, and decrease mortality in cancer patients and survivors. Interventions that improve access to these types of foods while lowering their cost, especially because of financial concerns among cancer patients and survivors, are paramount to improving outcomes among these populations.

Eliminating Alcohol and Tobacco Use

It has been estimated that 1.4 percent of adult cancer survivors smoked cigarettes in 2022 (265). Smoking among cancer survivors is associated with poor outcomes and greater treatment-related complications, higher risk of secondary cancers, lower HRQOL, and greater mortality (706,707). Cigarette smoking is also associated with greater cancer-related symptoms including fatigue, pain, and emotional problems among adults with cancer (736).

The use of e-cigarettes among cancer survivors has been on the rise. In 2017, 10.7 percent of cancer survivors used e-cigarettes compared to only 8.5 percent in 2014 (737). Currently, the rates of e-cigarette use among cancer survivors are estimated at 15 percent in 2024, with 63 percent of survivors who smoke traditional cigarettes also using e-cigarettes (738).

Smoking cessation can have immediate and long-term positive effects for cancer survivors. For instance, after smoking cessation, researchers observed a dramatic change in the immune properties of cancer patients and survivors toward a non–cancer-promoting profile (739).

It is concerning that cancer patients who are on active treatment are less likely to stop smoking or abstain from it, compared to those who have completed treatment (740). Decreasing dependence on smoking traditional cigarettes and e-cigarettes through smoking cessation programs can help to alleviate the increased burden that comes from using

SIDEBAR 43

What Is Palliative Care?

Palliative care is specialized care that provides, if needed, an extra layer of support to patients with and survivors of serious illnesses, such as cancer, and their families and caregivers.

Palliative care is given throughout a person's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care. Palliative care given near the end of life when curative treatment has stopped is usually referred to as hospice care.

Palliative care can be given in addition to cancer treatment or to those with no curative treatment options. Palliative care addresses many of the challenges that can affect quality of life after a cancer diagnosis, including:

- Emotional challenges, such as anxiety and depression.
- Physical symptoms and adverse effects of the disease and its treatment, such as pain, nausea, vomiting, fatigue, difficulty sleeping, and loss of appetite.
- Practical challenges, such as navigating the health care system.
- Spiritual challenges.

Source: (1).

these products. Smoking cessation programs that include both behavioral counseling and pharmacologic interventions have been shown to be the most effective in reducing smoking among cancer survivors (741). Further research is needed to identify effective methods to help cancer patients and survivors reduce dependence on tobacco products.

Consumption of alcohol can lead to adverse health and treatment outcomes among cancer patients and survivors, including increasing the risk of cancer recurrence. Unfortunately, 77.7 percent of individuals with a history of cancer report consuming alcohol (742). Among those who drink, 23.8 percent engage in binge drinking (greater than 6 drinks in one sitting), whereas 38.3 percent engage in hazardous drinking, as measured by the Alcohol Use Disorders Identification Test (742). While there are few interventions specifically developed for cancer survivors, cancer care providers should refer their patients with alcohol use disorder to evidence-based treatments, including behavioral counseling and/or pharmacotherapy, that have been developed for general populations. As heavy drinking among this population is associated with poor mental health and posttraumatic stress disorder, addressing the root causes of drinking is necessary. 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 treat the symptoms and side effects of any disease, including cancer, by addressing the physical, psychosocial, financial, and spiritual needs that arise from the disease and treatments (see **Sidebar 43**, p. 141). 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 (743).

Research shows that palliative care approaches improve pain management and reduce depression and functional limitations, improving the survivorship experience (744).

Cancer-focused organizations recommend integrating palliative care services early on in treatment (745-747). This ensures that the physical, psychosocial, and/or spiritual concerns of patients are addressed early, reducing negative outcomes and improving HRQOL.

Improving Mental Health

The psychological challenges faced by survivors of cancer necessitate approaches that improve the mental well-being of this population (see **Challenges Faced by Survivors**, p. 130). Several approaches can be utilized, including mind-body interventions, support groups, improved mental health screening, physical activity, and community engagement (748-751).

One approach is the use of "stepped care," which consistently evaluates how a patient is responding to both psychotherapy and medication every few weeks, emphasizing individualized treatment plans tailored for each patient. In one clinical trial that looked at outcomes of patients who participated in a stepped care program, researchers found that compared to those in a standard care group, patients in the stepped care model had more clinically meaningful improvements in HRQOL (752). This clinical trial also found that health care systems benefit from providing stepped care at no cost to the patient, as

SIDEBAR 44

Cancer Survivorship Experience and Personal Growth

Both quantitative and qualitative data demonstrate that most cancer survivors experience posttraumatic growth, which is described as the personal growth that comes from experiencing a stressful, traumatic event (754-756). Posttraumatic growth is not necessarily a consequence of a traumatic event and to experience posttraumatic growth, survivors need to cultivate these feelings through personal development (757). Posttraumatic growth is being more appreciated as an approach to improve a survivor's mental well-being and recovery. Components of posttraumatic growth include:

Relating to Others

Some survivors may find that their cancer diagnosis has helped them prioritize and improve relationships and build stronger connections with those who are important to them. These experiences are attributed to increased willingness to express feelings, understand complex emotions, and empathize better with those struggling with similar challenges.

New Possibilities

Some survivors may adapt a completely new lifestyle after cancer diagnosis, and may reevaluate their career or life path and choose to spend more time with family and friends. Change of lifestyle can often lead to healthier behaviors such as smoking cessation, engaging in a healthful diet, and exercising.

Personal Strength

Some survivors may experience a belief that if they are able to defeat cancer, they can possibly manage any future challenge. This can prompt positive attitudes during times of stress or anxiety.

New Appreciation of Life

Some survivors may reevaluate feelings of appreciation for good health as a second chance at life, and may feel grateful for the beauty in the world and importance of the small victories in life. Others may report having the perspective of living in the moment.

Spiritual Changes

Some survivors may find or strengthen spiritual beliefs and deepen their faith. Spiritual growth has also been shown to help survivors with their recovery and the ability to manage day-to-day challenges.

Source: (1).

underscored by the findings that this type of intervention led to savings of $16,000 per patient per year. This was due to shorter hospital stays, fewer emergency room visits, and fewer readmissions (752).

Researchers are also investigating how survivors of cancer experience posttraumatic growth, which describes positive life changes that can develop because of traumatic and stressful events, such as a diagnosis of cancer. Posttraumatic growth may lead to perceptions of new possibilities, closer relationships with family and friends, development of personal strength, spiritual development, and a greater appreciation for life (753). Although the concept of posttraumatic growth is not new, its potential in helping cancer survivors tackle the challenges of survivorship is only now being appreciated within the cancer care community. The most influential factors that affect posttraumatic growth include the level of social support and the use of various coping strategies among survivors of cancer (see **Sidebar 44**, p. 142).

Delivering Care to Cancer Survivors

Coordinating Care

The multifaced approach to treating cancer necessitates providing survivors with appropriate care to address their many needs, including transitioning from active treatment, coordinating follow-up appointments, addressing financial needs, and gaining access to other survivorship resources. Even when these resources are available, understanding how

SIDEBAR 45

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 (759). While patient navigation is being increasingly recognized as a potent resource for helping cancer survivors, challenges in implementation remain.

Benefits

Patient navigation bridges a variety of gaps and addresses diverse needs across the cancer care continuum:

- Patient navigation improves access to screening, patient care coordination, symptom management, and follow-up care (758, 760, 761).
- Patient navigation reduces the cost of health care by reducing emergency room visits and missed appointments (762-764).
- Patient navigation can reduce financial toxicity for patients with cancer (764).

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 Protection and Affordable Care Act in 2010, which helped increase access to patient navigation programs for cancer patients and survivors.
- In support of the White House's Cancer Moonshot initiative, the Centers for Medicare and Medicaid Services changed billing codes to allow oncologists to bill and receive Medicare payment for connecting patients to patient navigators as of January 1, 2024.

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.

or where to find them can be challenging. Coordination of care is required to help patients identify and gain access to such resources.

Coordinating cancer care is most effective when a designated individual or a team of people helps a cancer patient or survivor to gain access to the resources they need. A systematic review of studies conducted over 30 years found that coordination approaches led to improvements among 81 percent of survivors across multiple domains of cancer care, including screening, patient experience, and quality of end-of-life care (758).

Patient navigators and clinical care coordinators are individuals who help cancer patients and survivors access resources more effectively (see **Sidebar 45**, p. 143). Patient advocates, who are often cancer survivors themselves, are uniquely positioned to bridge critical gaps between patients, survivors, and the health care system.

Leveraging Patient Reported Outcomes

Patient reported outcomes (PROs), which are reports given by patients on their status that have not been interpreted by a clinician, are becoming more common, especially in clinical

trials, because they provide an unbiased, contextualized view of the patient experience (see **Sidebar 46**, p. 144). Incorporating the patient's perspective to understand treatment tolerability and efficacy in clinical trials will improve the cancer treatment experience for patients in the real world (765). Patient reported outcomes are collected through questionnaires, which alert clinicians to the status of the patient regarding HRQOL, symptoms, and health-related behaviors (e.g., smoking, diet, physical activity) (766). Patients engaged in monitoring their symptoms may have improved clinical outcomes and reduced risk of emergency room and hospital visits compared to those who do not complete these questionnaires (767,768). Integration of real-world electronic health records with PRO assessments that provide automated alerts to clinicians may help improve patient outcomes.

Use of patient reported outcomes in the Patient-Reported Outcomes Measurement Information System (PROMIS) study helped researchers identify issues surrounding psychosocial and quality of life matters among lung cancer survivors. The PROMIS study found that the most common issue faced by these individuals was reduced physical function and the interference of pain in their life. To improve patient-provider interactions and the quality of care that patients and survivors receive, the use of a screening program to identify patients with mental and physical issues as a result of their care is essential to alleviate these challenges (769).

SIDEBAR 46

Patient Reported Outcomes

Patient Reported Outcomes (PROs) are a way for a patient to report changes in quality of life or functional status associated with health care or treatment. Patient-reported measures are the tools used to measure PROs.

- PROs are **not interpreted by a physician** or anyone else and are a direct reflection of a patient's experience.
- PROs **can include health-related quality of life, functional status, symptom and symptom burden, personal experience of care,** and **other health conditions** such as anxiety and depression.
- PROs are **used in clinical trials** to reflect how a new drug may impact the patient, which can help inform how well or badly the drug is being tolerated.
- PROs are **being increasingly used by pharmaceutical companies** in the development of new therapeutics, which has the potential to improve the patient's experience and increase safety by placing the patients at the center of decision making.

Source: (1).

Supporting Caregivers

Caregivers comprise family members or friends who help patients with long-term chronic illness and manage any and all aspects of their care. One in five US adults (ages 18 to 64), accounting for over 53 million people, provided care for another person in 2020, a significant increase from 43.5 million in 2015 (770). It is further estimated that four million of these caregivers are caring for an adult cancer patient. More evidence of the challenges faced by caregivers is becoming clear and there are many opportunities to assist this vulnerable population.

In a study of cancer caregivers—specifically, informal caregivers—the average age of a caregiver was 58 years old. For many of these caregivers, helping a family member or friend with cancer takes a significant amount of time, with 40 percent of caregivers providing more than 40 hours of care per week, with most of that care devoted to activities, such as helping patients in and out of bed or chairs and help with using the restroom (771). Compared to other age groups, caregivers who are 65 and over experienced the highest level of physical, emotional, and financial burden (771). Compounding this issue is the lack of support for caregivers, with one study finding that only 16 percent of cancer clinics screened caregivers for distress and only 13 percent of those clinics had resources in place to assist caregivers (772). Survivors require many resources that are often provided by their caregivers, including arranging transportation, helping with day-to-day activities such as doctor visits, providing medical care or other clinical tasks, coordinating care, and giving emotional support. This often leads to burnout, which negatively impacts caregivers' psychological and emotional well-being. Identifying caregiver burnout is critical for providing early interventions and support to these individuals.

Financial toxicity among caregivers of family with chronic conditions including cancer has been well documented (773-776). A study of financial toxicity among patients with head and neck cancers and their caregivers found that while 26 percent of patients reported financial toxicity, 44.4 percent of caregivers reported financial toxicity (776).

Legislative efforts including 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 their National Strategy to Support Family Caregivers, which is a collaboration between federal and private partners to address the national need for comprehensive family caregiver support (777). Efforts to increase support for family cancer caregivers are urgently needed because nearly a quarter of Commission on Cancer–accredited US cancer centers do not have a family caregiver program (778).

Envisioning the Future of Cancer Science and Medicine

IN THIS SECTION, YOU WILL LEARN:

- The unprecedented advances against cancer in recent decades stem from breakthrough discoveries and technological advances across medicine.
- Radiotheranostics, a promising technique for detecting and treating cancer using radioisotopes, has shown remarkable success in treating multiple types of cancers simultaneously, marking a significant advancement in cancer treatment.
- Advances in noninvasive cancer imaging are revolutionizing visualization of tumor metabolism and assessment and monitoring of treatment response.
- Cancer engineering is emerging as a powerful interdisciplinary approach for understanding the complex nature of cancer to improve health outcomes.

The pace of progress against cancer has accelerated tremendously in recent years, as underscored throughout this report. Breakthrough discoveries and technological advances across the fields of science and medicine have substantially increased the understanding of cancer initiation and progression, providing the foundational knowledge for better strategies to reduce the risk of developing cancer, detect cancer at the earliest possible stage, and treat cancer effectively and more precisely. As a result, cancer deaths are declining, and cancer survivors are living longer and fuller lives.

The breadth of advances against cancer and their impact on saving and improving lives are a source of great optimism for cancer scientists, including the AACR president, 2024–2025, **Patricia M. LoRusso, DO, PhD (hc), FAACR** (see p. 149), who firmly believe that the fast-paced trajectory of progress against cancer can be further accelerated through sustained and predictable funding for cancer research.

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.

Cancer Engineering: An Interdisciplinary Approach to Drive Progress Against Cancer

Cancer engineering is an interdisciplinary field that combines principles from engineering, biology, and medicine to develop innovative approaches for the prevention, detection, diagnosis, and treatment of cancer (779). It involves the application of

SIDEBAR 47

Technological Innovations Emerging From Interdisciplinary Approaches

Cancer is a complex, multifaceted disease. Understanding cancer initiation and progression and developing effective strategies to detect, diagnose, and treat cancer require interdisciplinary approaches. Over the past decade, collaborations across the fields of biology, chemistry, engineering, and the physical sciences have yielded innovative technologies with immense potential to transform cancer research and care. Examples of the applications of these disciplines in cancer science and medicine are listed below:

Field	Application	In Cancer Research	In Patient Care
Nanotechnology (780)	Drug delivery	Using gold nanoparticles to target and kill tumor cells	Nanoparticles delivering drugs directly to the tumor, minimizing side effects on healthy tissues
Tissue Engineering (781)	Three-dimensional (3D) tumor models	Creating 3D models of tumors to study cancer progression and test novel treatments	Using 3D-printed scaffolds to support tissue regeneration after tumor removal
Biomaterials (782)	Drug delivery	Designing biomaterials to release anticancer drugs at controlled rates	Implantable biomaterials for localized chemotherapy delivery
Biomedical Imaging (783)	Enhanced imaging	Using advanced magnetic resonance imaging techniques to better visualize tumors	Improved positron emission tomography/computed tomography scans for early cancer detection
Systems Biology and Bioinformatics (784)	Data analysis	Using computational models to identify new therapeutic targets	Predicting responses to cancer therapies based on genomic, transcriptomic and proteomic data, among others
Microfluidics (785)	High-throughput screening	Developing microfluidic devices for screening cancer drugs	Lab-on-a-chip devices for rapid cancer diagnostics
Robotics and Automation (786)	Precise surgery	Robotic systems for conducting precise surgical removal of tumors	Automated biopsy analysis for faster diagnosis
Synthetic Biology (787)	Engineered cells	Engineering bacteria to produce anticancer compounds	Using modified immune cells to target and destroy cancer cells

engineering techniques and technologies to understand cancer biology and to create new tools and methods for combating the disease (see **Sidebar 47**, p. 147).

One of the most promising applications of cancer engineering is the precise delivery of targeted therapeutics

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Scan the QR code
to watch Dr. LoRusso's video interview.

Envisioning a Healthier Future for All Cancer Patients Through Clinical Research

Patricia M. LoRusso, DO, PhD (hc), FAACR

AACR President, 2024–2025

Professor of Medicine; Chief of the Early Phase Clinical Trials Program, Yale University; Associate Center Director of Experimental Therapeutics, Yale Cancer Center, New Haven, Connecticut

In the more than three decades that I have been in the cancer drug development arena, I have seen tremendous progress in the diagnosis and treatment of cancer. When I first started as a young investigator, there was only one chemotherapeutic available to treat metastatic colon cancer. Thanks to basic science unraveling many of the molecular alterations in cancer, we now have drugs that can even target specific subtypes of colorectal cancer.

Basic research is pivotal to progress against cancer. Without basic research, we would not be where we are today in diagnosing and treating patients with cancer.

Sequencing of the human genome and more specifically of tumors has unveiled targets that are responsible for cancer initiation and growth. As a result, researchers have made amazing advances in developing drugs against these targets, and patients have more treatment options available to them. For example, patients with lung cancer, even those with metastatic disease, have had significant improvements in their survival, because of precision medicine. And we continue to make significant progress for many other cancer types. We are also combining molecularly targeted therapeutics and immunotherapeutics to overcome treatment resistance and reduce toxicity.

Basic research is pivotal to progress against cancer. Without basic research, we would not be where we are today in diagnosing and treating patients with cancer. While it is important to translate from laboratory research to the clinic, it is also critical to bring clinical research back to the bench. For example, analyzing tumor samples from patients can help us understand why certain patients respond to a drug, while others do not. This continuum of bench to bedside back to bench is critical if we are going to improve outcomes for our patients.

When I first started in the clinic, most pediatric patients would die of acute lymphoblastic leukemia (ALL). In 2024, at least 85 percent of children with ALL are cured. One of the reasons for this progress is that over 60 to 70 percent of children with cancer are treated on clinical trials. We can study every patient to understand their disease to a greater extent. We need to keep the participation of children with cancer in clinical trials high and do better to increase clinical trial participation among adult patients.

Over the course of my academic career, clinical research has changed significantly, both in design and execution. We now need fewer patients to answer whether a drug is truly effective, in part, because of a better understanding of the biology of the disease. We are also increasingly bringing patient advocates into clinical practice. As many patient advocates have either lived through cancer or have cared for a patient with cancer, they bring more realistic viewpoints of what it takes to participate in a clinical trial.

Despite all the progress, we still have much work to do. The more we learn about cancer, the more we realize that it is a complex disease, and each patient is unique. We know that early detection of cancer is pivotal to reducing the burden of the disease. We need to invest more in early detection of cancer. There are also huge cancer disparities in the United States (US). Underrepresented populations, such as rural, Black, Hispanic, and LGBTQ communities, are faced with many challenges. These population groups do not have equitable access to treatments, diagnostics, and preventive interventions. Unfortunately, one of the drivers of these disparities is health care insurance, and many patients, often from underrepresented populations, are still uninsured.

Funding by the federal government in cancer research is pivotal to progress against cancer. The impact of the US taxpayers' investment in cancer research has been astronomical. However, the next step is the hardest. And it will require robust and sustained federal funding. I know that amazing strides against cancer will continue if we maintain our investment in medical research.

I truly believe that the future of cancer science and medicine is promising. Cancer diagnostics are becoming more sophisticated. New technologies, such as spatial transcriptomics, are helping us study tumors at a cellular level. Artificial intelligence–based approaches are beginning to transform cancer detection, diagnosis, treatment decision making and response monitoring. Convergence science, where we bring many disciplines together to leverage the astronomical amounts of patient data, is becoming an important aspect of cancer research for a more in-depth and integrated understanding of the disease and for developing the next generation of drugs.

I went into cancer research because I lost both of my parents to cancer when I was young. I recognized the personal challenges that come as a result of a loved one dying of cancer—and even though the pain dissipates with time, it never goes away. So, my dream is that one day cancer will become a chronic disease, even in patients with metastatic disease, and people will live much longer, healthier lives. What an impact it would have, not only for the patient or patient's family and friends, but also for the world, if that dream could come true.

to tumors. For example, nanotechnology, a cornerstone of cancer engineering, enables the creation of nanoparticles that can deliver drugs directly to cancer cells, sparing healthy tissues (780). Another way in which cancer engineering is accelerating the pace of progress against cancer is the development of advanced imaging techniques (see **A New Wave of Imaging Technologies**, p. 151). These imaging approaches can detect cancer at earlier stages and monitor treatment responses more accurately (783). Similarly, tissue engineering and biomaterials are revolutionizing cancer treatment by enabling the development of three-dimensional tumor models and implantable devices (781,782). These technologies allow researchers to study cancer in an environment that closely mimics the human body, facilitating the testing of new drugs and therapies. In the clinic, biomaterials can be used to create scaffolds that support tissue regeneration after tumor removal, improving patient recovery.

Because of the immense promise of cancer engineering, researchers have proposed conceptual frameworks to encourage interdisciplinary collaborations at institutional levels and accelerate further the pace of progress against cancer (779). It is important to note that realizing the promise of cancer engineering requires overcoming significant challenges, including financial and logistical barriers, as well as regulatory hurdles. Researchers are emphasizing the importance of education and training in cancer engineering to prepare a new generation of scientists with engineering expertise and a fundamental understanding of cancer biology to transform clinical cancer care (788). Continued interdisciplinary collaboration, investment in medical research, and a commitment to patient-centered research and care will be essential to harness the full potential of cancer engineering and improve outcomes for cancer patients.

A New Age of Radiation Therapy

Radiotherapy uses high-energy rays or particles to control the growth of and/or eradicate cancer cells by damaging their DNA (see **Advances in Radiation-based Approaches to Cancer Care**, p. 91). About 50 percent of all cancer patients in the United States receive radiotherapy as part of their treatment regimens (789). The number of cancer survivors who have received radiotherapy is projected to increase from 3.38 million in 2020 to 4.17 million in 2030 (422). Continued innovation and advances in radiotherapy are needed to minimize the adverse effects of the treatment while maximizing the benefits for patients.

Advances in Intraventricular Compartmental Radioimmunotherapy

Intraventricular compartmental radioimmunotherapy (cRIT) is a specialized form of radiotherapy for the treatment of certain types of cancer, particularly central nervous system tumors that are difficult to reach using other therapies. cRIT involves the development of antibodies that specifically target proteins present on the surface of cancer cells. These antibodies are labeled with a radioactive isotope and injected directly into the cerebrospinal fluid within the brain's ventricles using a specialized surgical instrument (790). Once injected, the radiolabeled antibodies bind to the cancer cells, and the radioactive isotopes attached to the antibodies help destroy cancer cells. Because the radiation emitted by the isotopes is localized to cancer cells, the radiation exposure to healthy tissue is minimal.

One of the cancer types for which cRIT has shown considerable effectiveness is medulloblastoma. Medulloblastoma is a type of brain tumor that originates in the cerebellum, the part of the brain located at the base of the skull. It arises in cells that are involved in motor control and coordination (791). Medulloblastoma is the most common type of malignant brain tumor in children, with a 10-year survival rate of 70 percent (792). Treatment options are limited to surgical removal of as much tissue as is safe, chemotherapy, and radiation of the entire brain and spinal cord; all of these options carry significant side effects (791).

Research has shown that the surface of cancer cells in patients with medulloblastoma (among other cancer types) carries a protein called B7-H3, which functions as a "brake" on the immune system (see **Sidebar 47, p.** 147) (793). The B7-H3 protein is an attractive target for drug development, and researchers have developed several antibodies directed against it (793). One such antibody, omburtamab, is chemically linked with the radioactive form of iodine (^{131}I) to make a cRT agent, called ^{131}I-Omburtamab (794). In a recent study, 20 patients with medulloblastoma were treated with cRIT. Injections of ^{131}I-Omburtamab once or twice monthly were associated with improved overall survival and survival without disease progression (795). Furthermore, six patients were alive with no evidence of disease 3 years after the treatment (795). This example highlights the potential of cRIT in improving health outcomes for patients with cancers.

THE INCIDENCE OF MEDULLOBLASTOMA
DURING 2016–2020 IN US CHILDREN AGES 0 TO 14 YEARS WAS 0.47 CASES PER 100,000, **AFFECTING ABOUT 300 CHILDREN EVERY YEAR.**

Source: (792).

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Despite its immense promise, cRIT presents some challenges. For example, cRIT requires precise delivery of radiolabeled antibodies through a complex surgical procedure. Consequently, a multidisciplinary team of oncologists, neurosurgeons, and radiologists is needed for the procedure and for careful monitoring of radiation doses. Furthermore, even though cRIT is a highly precise targeted therapy, the treatment can still cause neurotoxicity, or other complications related to radiation. Additional research is needed to further optimize cRIT for the benefit of patients with cancer.

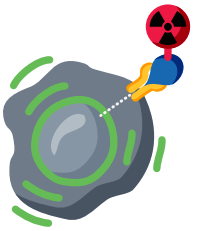
Emergence of Radiotheranostics

Radiotheranostics, also known as radiopharmaceutical therapy (RPT), refers to the combined imaging and precise delivery of radiopharmaceuticals to the tumor (796,797). Briefly, in RPT, cancer is visualized by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging using molecules that are linked to diagnostic radionuclides and bind to specific proteins on the surface of cancer cells or tumor microenvironment. Once the presence of cancer is confirmed, the same targeting agents—labeled with more potent therapeutic radioisotopes—are then used to kill cancer cells (798).

RPT has shown great promise in the clinic in treating various types of cancer, as evident from improved outcomes, lower side effects, and better quality of life compared to alternative therapies. The utility of RPT in cancer treatment is further underscored by the approval of several radiopharmaceuticals by the US Food and Drug Administration (FDA) in recent years, including a first-in-class combination of a radiodiagnostic and a radiotherapeutic agent to treat metastatic prostate cancer (84).

In addition to using RPT to treat advanced-stage cancers, researchers are testing RPT approaches as initial treatments and to treat earlier stages of the disease (see **Advances in Radiation-based Approaches to Cancer Care**, p. 91) (799). For example, findings from a phase I/II clinical trial show that when given before surgery to patients with prostate cancer whose tumor had not metastasized, RPT safely and precisely delivered radiation to tumors and, in about half of the patients, decreased the levels of prostate-specific antigen, a biomarker for prostate cancer, by half. Importantly, patients experienced minimal treatment-related adverse events, and surgery was safe with a low rate of complications (800). As researchers develop new and more sophisticated ways to deliver an expanding array of diagnostic and therapeutic radioisotopes, a number of clinical trials are underway to test the efficacy and safety of radiotheranostic pairs, alone or in combination with other types of cancer treatments, for treating multiple cancer types (see **Table 8**, p. 152) (797,799). While advances in RPT offer exciting new frontiers for progress against cancer, some challenges remain, such as production and supply of radiotheranostic agents, patients' access to RPT, and training of the workforce to administer this highly specialized form of cancer treatment, among others (797,801-803).

RADIOTHERANOSTICS TO VISUALIZE AND KILL METASTATIC PROSTATE CANCER:



FDA APPROVED

To visualize prostate cancer cells with prostate-specific membrane antigen (PSMA)—**diagnostic agent gallium Ga-68 gozetotide** (Locametz)

FDA APPROVED

To kill prostate cancer cells with PSMA—**therapeutic agent lutetium Lu-177 vipivotide tetraxetan** (Pluvicto)

Source: (84).

W49

A New Wave of Imaging Technologies

Imaging has revolutionized cancer diagnosis and treatment by providing noninvasive methods to visualize tumors, monitor their progression, and guide therapeutic interventions. Some of the most used imaging approaches in cancer care include X-ray imaging, SPECT, PET, computed tomography (CT) and magnetic resonance imaging (MRI) (796). These techniques enable early detection, accurate staging, and monitoring of treatment response, significantly improving patient outcomes.

Visualizing Tumor Metabolism Better

PET is an imaging technique that provides detailed information about the metabolic and functional activities within the body. PET is performed by injecting a tracer molecule, typically a form of glucose labeled with a radioactive isotope, into a patient's bloodstream. Because of higher metabolism, cancer cells absorb a higher amount of the tracer molecule than normal cells. The radioactive isotope interacts with electrons in the body to produce gamma rays that are detected by PET scanners. Using images captured by PET scanners, a detailed three-dimensional map of the patient's body is constructed, with areas of high metabolism indicating the presence of tumors (804). PET is widely used in

TABLE 8

A Selected List of Radiotheranostic Pairs Currently Being Tested in Clinical Trials to Treat Different Types of Cancer

CANCER TYPE	TARGET	DIAGNOSTIC RADIONUCLIDE	THERAPEUTIC RADIONUCLIDE	TRIAL PHASE
AML, CML, MDS	CD45	^{123}I, ^{124}I, ^{131}I	^{131}I	I/III
Metastatic liver	SSTR	^{68}Ga	^{213}Bi	I
Metastatic neuroendocrine	SSTR	^{68}Ga, ^{18}F	^{90}Y, ^{177}Lu, ^{225}Ac	I/II
Metastatic prostate	PSMA	^{68}Ga, ^{64}Cu	^{177}Lu, ^{67}Cu, ^{225}Ac	I/III
Metastatic prostate (with enzalutamide)	PSMA	^{68}Ga, ^{18}F	^{177}Lu, ^{131}I	I/II/III
Neuroendocrine, lung (small cell), breast	SSTR	^{68}Ga, ^{18}F	^{177}Lu	I/II
Non-Hodgkin lymphoma	CD37	^{68}Ga	^{177}Lu	I/II
Pancreatic, colorectal, gastric	Neurotensin receptor type 1	^{68}Ga	^{177}Lu	I/II
Prostate	GRPR/bombesin receptor	^{68}Ga, ^{64}Cu	^{177}Lu, ^{67}Cu	I
Thyroid	Sodium iodide symporter	^{123}I, ^{124}I, ^{131}I	^{131}I	I/II/III

AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; CD, cluster of differentiation; SSTR, somatostatin receptor; PSMA, prostate-specific membrane antigen; GRPR, gastric-releasing peptide receptor; I, iodine; Ga, gallium; Bi, bismuth; F, fluorine; Y, yttrium; Lu, lutetium; Cu, copper.
Source: (797,799).

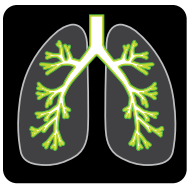
cancer diagnosis, staging, and monitoring treatment response. However, a drawback of PET is exposure of the patient to radiation, especially when repeated scans are necessary to accurately detect tumors, although the radiation dose is still less than that of diagnostic CT scans (804).

Researchers are continually innovating PET to maximize its benefits for patients, while minimizing potential harm (783). An important recent development in this regard is the development of PET scanners that can cover much larger portions of the body in a single scan (805,806). This new generation of PET scanners can image the entire body or large sections of it simultaneously. This is beneficial for patients in several ways, including reduced radiation exposure, improved image quality, and decreased scan time (806-808). Furthermore, the ability to image the entire body or large sections of it also allows researchers to study the efficacy of new and novel radiopharmaceutical agents quickly (805,808).

Because PET primarily captures metabolic activity or target expression with high accuracy, it is often combined with other imaging approaches, such as CT (809) or MRI (810,811), to simultaneously capture high-resolution anatomic information for enhanced diagnostic accuracy. Thus, combined PET-MRI scans help develop highly detailed and precise 3D maps of the body. This precision has led to exciting recent developments in cancer imaging in which researchers are using the combined PET-MRI scans for predicting outcomes in patients with lymphoma after CAR T-cell therapy (812), identifying lesions inside the prostate gland (813), and predicting overall survival in patients with glioma (814). Another way researchers are exploring the utility of combined PET-CT is imaging tumors during surgery for a more precise assessment of tumor margins (815).

In addition to improved PET approaches discussed here, two other recent advances to capture dynamic changes in tumor metabolism are hyperpolarized MRI and deuterium metabolic imaging (817). Hyperpolarized MRI uses specialized imaging agents to significantly enhance the MRI signal, while deuterium metabolic imaging uses deuterium, a stable and non-radioactive form of hydrogen, to map and visualize metabolic processes within the body. Because of

In December 2022, FDA approved XENOVIEW for use in adults and children age 12 and older. **XENOVIEW is an imaging agent specially designed to enhance scan quality** and is inhaled to evaluate lung ventilation using MRI-CT.



Source: (816).

W50

higher precision in detecting tumors and visualizing tumor metabolism, and because of the absence of ionizing radiation which can cause DNA damage, both approaches have the potential to revolutionize the assessment of cancer metabolism (see **Sidebar 32**, p. 96) (818).

Monitoring Treatment Response Effectively

Cancer diagnosis and treatment have evolved significantly over the past decades, driven by advances in molecular biology and imaging technologies. One of the most promising developments in this field is the use of molecular imaging agents as companion diagnostics. These agents can be visualized using PET, MRI, single-photon emission computed tomography (SPECT), and optical imaging, and provide critical insights into the molecular characteristics of tumors, helping to identify patients who are most likely to benefit from specific therapies, monitor treatment responses, and detect resistance mechanisms.

A key advantage of molecular imaging agents is the dynamic assessment of the effectiveness of treatment by measuring changes in tumor metabolism, proliferation, immune response, and presence or abundance of certain proteins on the surface of cancer cells. Over the past decade, researchers have developed many new molecular imaging agents that are being tested in preclinical research models. One example of such molecular imaging agents is the fibroblast activation protein inhibitor (FAPI) (819), which binds to FAP, a protein that is abundantly present on the surface of cells present in the tumor microenvironment of more than 90 percent of epithelial tumors, and on the cell surfaces of some tumors, such as sarcomas (820). In cancer imaging, researchers are using versions of FAPI conjugated with radioisotopes (e.g., ^{68}Ga) to evaluate characteristics of a number of cancer types, including pancreatic, colorectal, and breast cancer (821-823). Another group of molecules being used for molecular imaging as companion diagnostics consists of antibodies against proteins present on the surface of cancer cells and linked with imaging agents (824).

The integration of molecular imaging agents as companion diagnostics is the next frontier in cancer imaging that is helping researchers visualize tumors noninvasively. In the clinic, the use of these agents is guiding treatment decisions and monitoring patients' responses to treatments. For example, SC16.56 is an antibody directed against a protein called delta-like ligand 3 (DLL3), which is abundantly present in certain types of tumors, including cancers of lung, liver, and breast and neuroendocrine tumors (825). When chemically linked with a radioactive form of zirconium, the resulting imaging agent, [^{89}Zr]Zr-DFO-SC16.56, can detect DLL3-expressing tumors (826). In a recent study, researchers successfully used [^{89}Zr]Zr-DFO-SC16.56 for the first time to noninvasively image DLL3-expressing neuroendocrine tumors inside the human body (827). This advance can significantly help develop approaches to select patients who are eligible for certain treatments and test the efficacy of new treatments targeted against DLL3-expressing tumors using a precision-medicine approach, which is an intense area of focus (828,829).

As the clinical use of radiolabeled imaging agents as companion diagnostics gains traction, it is important to note that the development and approval of these agents in the clinic require extensive validation. Furthermore, the need for a specialized infrastructure and workforce can significantly limit their availability and utilization, similar to other specialized imaging techniques (e.g., MRI), and may contribute to cancer disparities. Finally, because these agents are radioactive, similar to CT scans, repeated imaging may pose potential risks, especially for children, adolescent, and young adult patients, and their use should be balanced with the benefits gained with the information obtained (830).

Advancing Cancer Research and Patient Care Through Evidence-based Policies

IN THIS SECTION, YOU WILL LEARN:

- Robust investment in federal agencies, including NIH and NCI, is vital to making further progress, including improvements in cancer screening, treatment, and survivorship.
- Support is needed for education and training programs to ensure that the United States has a strong medical research and clinical workforce that is broadly representative of society.
- FDA plays a central role in expediting the availability of safe and effective cancer therapies, including through the expansion and diversification of clinical trials.
- Federal agencies, including NIH, CDC, AHRQ, and EPA, and many of their programs are crucial for reducing the risk of cancer and eliminating cancer disparities.

The tremendous progress we have made against cancer over the past several decades has depended on strong federal investments in medical and public health research. Important federal programs in cancer prevention, early detection, and treatment are funded and managed by many different agencies, including the National Institutes of Health (NIH), the National Cancer Institute (NCI), the US Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the Department of Veterans Affairs (VA), and the Environmental Protection Agency (EPA).

Despite the importance of these federal efforts, the 2023 Fiscal Responsibility Act places strict caps on federal domestic spending (including funding for research and health programs) in fiscal year (FY) 2024 and FY 2025 (831). These funding constraints are already curtailing important scientific progress (832). It will therefore be critical that Congress lift these spending caps and provide robust, sustained, and predictable funding for the federal agencies that are crucial for the fight against cancer.

Investments in Research for a Healthier Future

The US Department of Health and Human Services (HHS) contains a rich ecosystem of agencies, such as NIH, dedicated to advancing medical research. As the world's largest public funder of medical science (833), NIH provides funding for research projects and clinical trials across the nation that aim to promote the prevention, diagnosis, and treatment of various medical conditions.

The largest of the 27 institutes and centers within NIH is NCI, whose main focus is to support cancer research and help train cancer researchers (834). An additional component of NIH, the Advanced Research Projects Agency for Health (ARPA-H), funds and empowers high-potential, high-impact medical research projects that cannot be realized through traditional commercial or research means (835).

FDA is another HHS agency that plays a major role in supporting efforts to prevent and treat cancer. Two key FDA centers assist in this mission: the Oncology Center for Excellence (OCE), which brings together leading researchers to conduct expedited reviews of cancer-related medical products (836); and the Center for Tobacco Products (CTP) (837), which enforces laws and regulations on tobacco products that cause cancer.

Also a part of HHS, AHRQ supports health care access and research by collecting survey data and assisting with the development of guidelines for screening and preventative services. AHRQ additionally offers intramural and extramural predoctoral and postdoctoral grants to improve education and career development opportunities for health services researchers (838).

As the nation's leading public health agency, CDC plays an essential role in cancer prevention and research to promote public health. Its Division of Cancer Prevention and Control leads efforts to collect data on cancer cases, promote cancer screenings, and fund cancer prevention programs (839). CDC funds the North American Association of Central Cancer Registries (NAACCR) program, a core cancer surveillance system across the United States. This coordinated data collection effort is vital to advance cancer research and develop more effective public health interventions (840). Beyond cancer-specific programs, CDC funds public health capacity and workforce training across the nation through grants to state and local public health departments (841). These investments also increase access to screening and prevention programs and improve data collection in the fight against cancer. As alluded to by **Congresswoman Madeleine Dean**, these investments also increase access to screening and prevention programs and improve data collection in the fight against cancer.

Continued investment in these agencies that advance medical research and public health is of vital importance to the nation. These investments have improved health outcomes for patients with cancer, resulting in a drop in the cancer mortality rate. As of 2021, the age-adjusted cancer death rate has declined by 33 percent since reaching its peak in 1991 (2). This decline would not have been possible without the development of life-saving cancer treatments. For example, between 2010 and 2019, NIH funding contributed to 354 of 356 new FDA-approved drugs, including 86 first in class products to treat cancer and other diseases. Furthermore, the National Breast and Cervical Cancer Early Detection and Screening Program (NBCCEDP), the Colorectal Cancer Control Program, and other programs have contributed to the downward trend in cancer deaths by allowing people who are uninsured or underinsured to access free screening services.

Despite significant progress in improving cancer-related health outcomes, there are concerning trends related to cancer incidence that underscore the need to continue prioritizing investments in medical research. Six common cancers—breast, prostate, endometrial, pancreatic, kidney, and melanoma—have seen diagnoses increase in recent years, which can be attributed to an aging and a growing population. There are also alarming increases in the incidence and mortality of certain cancers in younger people, notably those of colorectal cancer in people between ages 18 and 49 (842). As a result, the number of new cancer diagnoses in the United States is projected to surpass two million in 2024, the first time that such a threshold has been reached (2). Thus, continued investment in medical research will only become more important as the number of Americans diagnosed with cancer continues to rise.

The Honorable Madeleine Dean

US REPRESENTATIVE FOR PENNSYLVANIA'S 4TH DISTRICT

Every family has been altered by cancer in some way. In my family, we lost my beautiful mother, Mary, to ovarian cancer at what should have been just the midpoint of her life. Her passing was devastatingly fast and we were left in shock by such an enormous loss. We also lost my dear Uncle Larry to cancer. So together, we've mourned cancer claiming loved ones and we know our story is a story many others share.

Yet, two of my brothers caught skin cancer early and their doctors were able to take care of them. These are the stories we must strive for—the stories of hope and relief.

My family members inform my work as a lawmaker. In Congress, we have an obligation to fight for the millions of Americans waging battles with this devastating disease—that means supporting prevention, screening, and research. Every person deserves quality, affordable health care.

The scientists and physicians are leading this fight—and I'm deeply grateful for their commitment. In Congress, I'll continue to support their efforts through federal funding, expansion of testing, and raising awareness. They save lives.

Additionally, investment in medical research immensely benefits the US economy. NIH-awarded funding for extramural research supports the purchase of services, goods, and materials across the nation, which helps to generate new employment opportunities and economic growth. In FY 2023, NIH awarded $37.81 billion to investigators in all 50 states and the District of Columbia to conduct extramural research. This funding directly and indirectly supported 412,041 new jobs and yielded $92.89 billion in economic activity. Furthermore, robust funding for NIH helps ensure that the United States continues to be a global leader in medical research and innovation (843).

Continued investment in medical research and public health is also a matter of national security. Infectious diseases, such as COVID-19, can threaten military readiness due to their potential to temporarily incapacitate or disable both current and potential armed services personnel (844). Fortunately, decades of NIH-supported research, including NCI-supported research on the immune system, contributed to the development of COVID-19 vaccines (24,845,846), which are effective in limiting the spread of SARS-CoV-2 infections, hospitalizations and deaths (847), and infection-associated chronic conditions known as long COVID (848). Therefore, support for NIH funding is an asset for national security.

Beyond vaccine development, investment in public health infrastructure is essential to ensure that threats to public health can be swiftly addressed. Currently, CDC supports two preparedness programs that provide states, localities, and territories with funding to support a skilled public health workforce and physical infrastructure, such as laboratories. These programs played a key role in deploying vaccines during the COVID-19 pandemic.

In recognition of these benefits, the Biden administration supports additional investments in medical research in fiscal year (FY) 2025. Released in March 2024, the president's FY 2025 Budget Request calls for $48.3 billion for the base NIH budget, which amounts to a $1.2 billion or 2.7 percent increase over FY 2024 funding. Additionally, the budget proposes $7.8 billion in FY 2025 funding for NCI, a $615 million increase over the FY 2024 level. Also under the NIH umbrella, ARPA-H would receive $1.5 billion per the administration's FY 2025 request, which is the same amount the agency received in FY 2024.

The White House budget would reinvest in the Cancer Moonshot, proposing more than $2 billion for programs aimed at cutting the cancer death rate by at least 50 percent over the next 25 years (849). Initially launched in 2016, funding for the Cancer Moonshot expired in 2023. This initiative has provided significant additional funding for NCI to support more cancer research opportunities (850). For example, Moonshot-supported programs such as the Immuno-Oncology Translational Network and the Pancreatic Cancer Microenvironment Network have contributed to progress against cancer by facilitating the discovery of new immune system targets for cancer therapies.

Despite support from the White House, medical research funding faces a difficult budgetary environment as the FY 2025 appropriations process unfolds. Finalized in March 2024, the Consolidated Appropriations Act 2024, provided NIH and NCI with $47.1 billion and $7.2 billion, respectively, amounting to reductions of $378 million and $96 million compared to FY 2023 levels (831). This marks the first occasion since FY 2014 that Congress did not appropriate additional funds for NIH (851).

The primary reason for the lack of a funding increase for NIH in FY 2024 was the establishment of caps on discretionary defense and nondefense spending imposed in June 2023 as part of an agreement to raise the debt ceiling (852). Combined with a decrease in funding from the 21st Century Cures Act (including the expiration of the Cancer Moonshot funding), these spending caps resulted in the decrease in NIH appropriations for the current fiscal year.

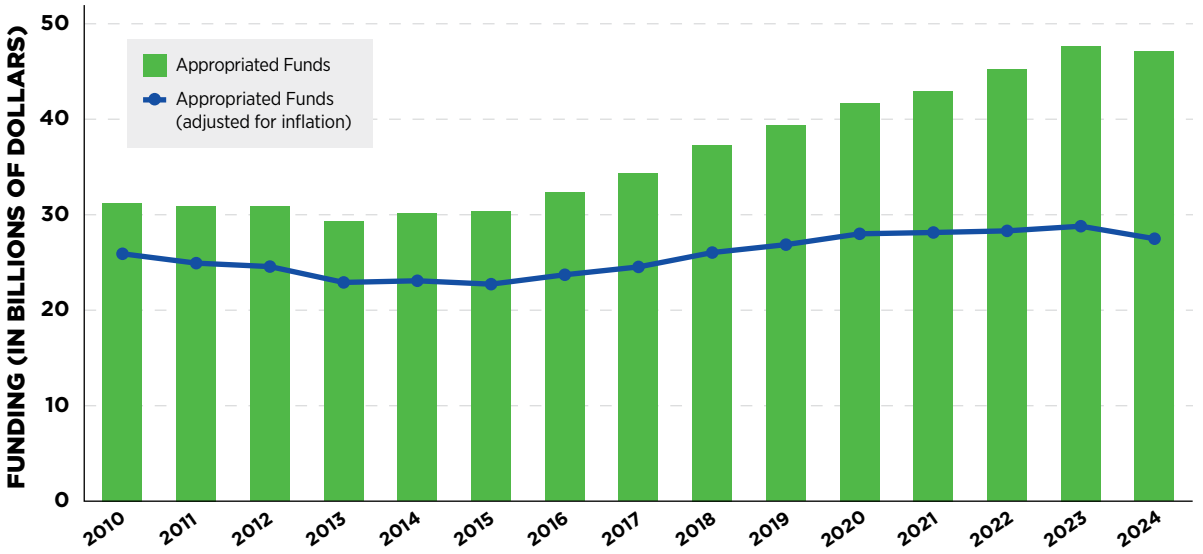
Flat or declining funding for medical research can set a precedent for lower funding in coming years because the FY 2026 budget will be built on the FY 2025 final budget as a baseline. Additionally, flat funding is further damaging to science due to the increased costs of conducting research brought about by inflation (see **Figure 21**, p. 157).

The caps on discretionary nondefense spending do not expire until September 30, 2025, which means they will continue to put downward pressure on investments in NIH and other discretionary nondefense priorities that support medical research and health. Adding to the difficulties facing the FY 2025 appropriations process is the 2024 general election on November 5, 2024, which will determine control of the presidency, the House of Representatives, and the Senate. As a result, Congress is likely to delay final decisions on FY 2025 appropriations bills until after federal election results have been determined.

Furthermore, partisan differences over federal appropriations could cloud prospects for greater investments in medical research in FY 2025. Senate Appropriations Committee Chair Patty Murray (D-WA) and Ranking Member Susan Collins (R-ME) remain committed to a bipartisan approach to FY 2025 appropriations to ensure that investments in NIH and NCI continue to grow. However, some House Republicans are demanding strong adherence to the spending caps as well as additional cuts to discretionary nondefense spending. As a result, advocates for stronger investments in medical research are likely to encounter a contentious appropriations environment in FY 2025.

FIGURE 21

NIH Funding and the Importance of Continuing Robust Increases



Funding for the National Institutes of Health (NIH) stagnated in the early 2010s. When adjusted for inflation, these years of flat funding represented a decline in the nation's capacity to fund biomedical research and training (line). Appropriations increases between 2016 and 2023 began to rebuild the agency's budget in inflation adjusted terms, but the NIH budget fell again in 2024. Complete histories of the appropriated funds and the biomedical research and development price index can be accessed at: https://officeofbudget.od.nih.gov/

A Diverse Cancer Research and Care Workforce Drives Innovation

Further progress in cancer research and patient care will require a robust and diverse scientific and clinical workforce. Diversity strengthens scientific collaborations, and progress toward health equity depends on educating a health care workforce that is broadly representative of society (853-856). However, many structural barriers remain that lead to a lack of diversity and representation in research, medicine, and other health care fields, as highlighted in the *AACR Cancer Disparities Progress Report 2024* (29).

Programs to Expand and Diversify the Scientific Research Workforce

In recent years, many federal initiatives have been undertaken to further broaden participation in Science, Technology, Engineering, Mathematics, and Medicine (STEMM). The National Science Foundation (NSF), an independent federal agency that does not fall under any cabinet within the executive branch, funds a broad portfolio of basic and applied research programs as well as an extensive series of STEMM education and training programs, including support for K–12 education, undergraduate and graduate students, postdoctoral fellows, faculty, and other members of the scientific and technical workforce (857,858). Broadening representation and participation in the sciences, engineering, and medicine is a major part of the NSF (859)mission.

Several NSF programs aimed at diversifying the scientific workforce were either created or enhanced by provisions of the 2022 Creating Helpful Incentives to Produce Semiconductors (CHIPS) and Science Act, including new initiatives to bolster programs at Historically Black Colleges and Universities (HBCUs) and other minority-serving institutions (MSIs), create new research and educational opportunities across diverse geographies, and combat sexual and gender harassment in research settings (860,861). Despite the scale and ambition of these initiatives, Congress has funded them far below the levels authorized by the CHIPS and Science Act (862).

NIH has also taken a multi-faceted approach in its efforts to create a more inclusive medical workforce. The NIH UNITE

initiative is an agency-wide effort to dismantle structural racism within the NIH and across the medical research community. The initiative has four focus areas: expanding health disparities research, promoting equity and inclusion within NIH, promoting equity in the extramural medical community, and improving the collection and dissemination of racial and ethnic equity data (863). The Office of the Chief Officer for Scientific Workforce Diversity (COSWD) plays a key role in the advancement of scientific training, diversity, and inclusion in the medical research workforce.

COSWD programs include administrative supplements to existing NIH awards to support Diversity, Equity, Inclusion, and Accessibility (DEIA) mentorship activities; a prize competition for institutions implementing novel DEIA programs; and the NIH Distinguished Scholars Program, designed to promote and enhance DEIA within the NIH intramural program (864). Each Institute and Center (IC) within NIH, including NCI, also has a wide range of education and career development programs aimed at enhancing workforce training specific to the disciplinary focus of each respective IC (865).

To expand and diversify the cancer research workforce, NCI implements and manages a range of policies and programs (866). Beginning in 2021, NCI began requiring a Plan to Enhance Diversity (PED) as a core component of the application for a Cancer Center Support Grant, the major source of support for NCI-Designated Cancer Centers (867). As part of their PEDs, NCI-designated centers are directed to implement plans that boost diversity and representation among cancer center leadership; foster the careers of diverse junior, early, and mid-career scientists; and establish criteria for measuring progress. The establishment of the PED requirement has been important for the creation of new recruitment, training, and mentoring initiatives at cancer institutes; however, more work and resources will be needed to maximize the effectiveness of PEDs (868).

Within NCI, the Center for Cancer Health Equity (CCHE) leads initiatives to improve diversity and representation in cancer research. It funds a broad portfolio of programs that support education and mentoring of students and trainees at all levels; fosters opportunities for scientists from diverse backgrounds to become independent scientific investigators; and partners with academic institutions serving populations subjected to health disparities and underrepresented students (see **Sidebar 48**, p. 159) (29,869).

Unfortunately, the Supreme Court decision in June 2023, which struck down affirmative action policies in university admissions, will likely have a detrimental effect on broadening participation in scientific and medical training. Prior to the June 2023 ruling, state bans on the use of race in academic admission had caused enrollment of members of racial minorities to drop at public universities (870). Similar outcomes are expected as universities shift their policies to align with the Court's ruling (871).

Another area of concern for the future health of the cancer research enterprise is the decline in the number of postdoctoral fellows, particularly in the biological and medical sciences (872). Postdoctoral researchers are an essential part of the biomedical workforce, and postdoctoral experience is typical for life scientists who go on to have careers in academic research. However, postdoctoral fellows typically receive low compensation relative to their professional training, and often face job insecurity and uneven opportunities for mentorship and career advancement; these issues are further exacerbated for postdoctoral fellows from historically underrepresented or marginalized groups (873). Given these problems, many biomedical scientists who might have pursued postdoctoral training are choosing alternative career opportunities in the pharmaceutical or biotechnology industries (874). Scientists in industry make important contributions to the advancement of new cancer therapeutics and other technologies, but the health of the biomedical workforce and the well-being of individual scientists will depend on reforms to the postdoctoral system. To this end, NIH has adopted recommendations from an advisory committee on ways to improve financial support, working environments, career advancement, and other aspects of the postdoctoral experience (875).

Programs to Strengthen and Expand the Health Care Workforce

Breakthroughs in medical and public health research can further benefit the populace if there is a robust medical and health care workforce that reflects the diversity of society. However, population groups underrepresented in the biomedical workforce face many barriers to educational opportunities and, in turn, full and equitable participation in health care professions, including physicians, physician-scientists, and nurses (29).

Many of the NIH and NCI programs described in this chapter are also working to address shortcomings in cancer care (particularly regarding medical professionals who conduct basic, translational, and clinical research), though more robust federal support is needed. Importantly, Medicare is the largest source of funding in the United States for graduate medical education (MD or the equivalent), supporting approximately 98,000 medical residency positions (876,877). Under current law, however, the number of residency positions is capped at approximately the same number as in 1996 (980). The same cap on Medicare funding for residencies also applies to

SIDEBAR 48

National Cancer Institute (NCI) Programs Promoting a Diverse Scientific Workforce

NCI's Center for Cancer Health Equity (CCHE) is committed to a cancer research workforce representative of the communities that experience disproportionate risk for and burden across the cancer continuum. Some of CCHE initiatives and programs include:

The Diversity Career Development Program (DCDP) provides current NCI postdoctoral fellows with the tools necessary to develop as leaders in academic independent research careers.

The Frederick Diversity Committee (FDC) provides current NCI fellows with opportunities to promote diversity and inclusivity at the Frederick campus.

Black Cancer Researchers (BCR) aims to build community among the three NCI campuses and create a safe informal space for Black scientists within the agency.

The Continuing Umbrella of Research Experiences (CURE) Program offers unique training and career development opportunities to enhance and increase diversity in the cancer and cancer health disparities research workforce.

Partnerships to Advance Cancer Health Equity (PACHE), a CURE program, focuses on promoting diversity in the cancer research workforce.

The Intramural Continuing Umbrella of Research Experiences (iCURE) program provides mentored research experiences for underrepresented students and scientists from diverse backgrounds in the multidisciplinary research environment of the three NCI campuses.

R25 Youth Enjoy Science Program (YES), the only early-intervention program at NCI, supports research education activities that encourage students from diverse backgrounds in grades 6–12 and undergraduates to pursue further studies or careers in research.

Cancer Moonshot Scholars program aims to enhance the diversity of the cancer research workforce while bringing in new ideas and perspectives.

The Administrative Supplement to Promote Diversity supports candidates from underrepresented backgrounds in cancer research by offering financial assistance to students and research scientists seeking practical experience with established researchers who serve as mentors.

Transformative Educational Advancement and Mentoring (TEAM) Network addresses institutional barriers by piloting the use of training champions (TCs) at Minority-Serving Institutions (MSIs) to promote education and career development opportunities for diverse scholars.

The Early Investigator Advancement Program (EIAP), a cross-NCI initiative, seeks to enhance diversity in the cancer research workforce by providing in-kind grantsmanship training, individualized grantsmanship coaching, career navigation, mentorship from NCI-funded established investigators, peer networking opportunities, access to professional development workshops (PDWs), and professional development webinars.

The Cancer Research Interns (CRI) Summer Program provides a training opportunity for students looking for initial research training.

The Cancer Research Postbac (CRP) Program provides up to 2 years of postbaccalaureate training to explore opportunities in basic and clinical research, cancer epidemiology and genetics research, cancer control science, and global health.

NCI Postdoc Recruitment Event (PRE) provides doctoral candidates with the opportunity to explore postdoctoral opportunities at NCI.

medical fellowships, limiting the number of publicly funded specialty training opportunities for physicians (878). Given the growth of the US population and the increased demand for medical care, this cap is a significant obstacle, especially given the shortages of physicians in rural and underserved communities (879).

More support is also needed for cancer prevention training. Programs such as the NCI Cancer Prevention Fellowship Program (CPFP) provide opportunities for fellows to pursue research projects related to cancer prevention (880), and many universities have academic programs focused on prevention (881-884). However, these efforts are somewhat

limited in scale. Initiatives such as partnerships between Health Resources and Services Administration (HRSA)–funded community health centers and NCI-designated Cancer Centers may provide opportunities to leverage federal resources to expand the training of health care professionals focused on cancer prevention (885).

Ensuring Safe and Effective Cancer Therapies Through Regulatory Science

FDA is the principal agency responsible for ensuring that medicines are safe and effective. Its regulatory oversight spans the entire process of drug development—from translational laboratory studies to clinical trials and post-marketing evaluation. In recent years, drug development, particularly for cancer, has become increasingly complex and often involves multiple stakeholders across the globe. To streamline the process, FDA's Oncology Center of Excellence (OCE) was established in 2017 under the 21st Century Cures Act and collaborates with three FDA product centers: the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH). This multi-center effort seeks to expedite the availability of new cancer therapies by integrating reviews and advancing regulatory science and policy. Since OCE's first drug approval in 2017, 174 new anticancer therapies for solid tumors have been approved. In comparison, the agency only approved 71 therapies for adults with solid tumors from 2002 to 2016 (886). FDA relies on funding from Congress and congressionally authorized user fees paid by the pharmaceutical industry to implement these initiatives. This funding is crucial to support FDA's mission, keep pace with evolving regulatory science, and advance progress in cancer research and treatment.

Diversifying and Decentralizing Trials

In recent decades, clinical trials have played a pivotal role in driving medical and scientific progress by introducing innovative treatments and deepening our understanding of cancer. Although most patients express interest in participating in cancer clinical trials, a small percentage of people with cancer or at risk for cancer participate in clinical trials today. Only 8 percent of adults with cancer participate in clinical trials (489). These percentages are even lower for many groups historically underrepresented in clinical research (887). Low participation rates can be attributed to structural barriers, which include narrow eligibility criteria and inaccessibility, study burden, distrust, lack of awareness, and fear (888).

The COVID-19 pandemic exacerbated these disparities, which triggered the need to develop innovative ways to recruit and retain participants for clinical studies. Conducting virtual appointments between health care providers and patients was fundamental to providing continuous care and accelerated the transition to decentralized trials (889). Decentralizing clinical trial operations allows trial participation from home, which can be implemented using digital health technologies, including wearable devices, mobile health apps, and platforms for telemedicine.

FDA has taken additional steps to support decentralized clinical trials (DCTs) and in May 2023 released draft guidance providing recommendations for their use. In the guidance, FDA provides design considerations for DCTs, conduct of remote clinical trial visits, and the use of digital health technologies for remote data collection (890). Another key element in the guidance focuses on the trial sponsor's responsibility to include diverse groups in their study populations—a longstanding commitment of the agency.

FDA has developed numerous patient-centered initiatives, including Project Equity, which aims to improve access to cancer clinical trials for historically underrepresented populations, and Project Silver, which focuses on increasing representation of older adults in cancer research (891). In addition, FDA has issued multiple guidance documents offering recommendations that may bolster diversity within cancer clinical studies. Most recently, FDA issued guidance on Diversity Action Plans in June 2024 aimed at enhancing the recruitment of participants from underrepresented populations in clinical studies. This new guidance replaces FDA's previous draft from April 2022, fulfilling a mandate under the Food and Drug Omnibus Reform Act of 2022 (FDORA) to outline the structure and details of Diversity Action Plans (892,893). The plan recommends inclusion of underrepresented populations that reflect different races and ethnicities, age groups, sexes at birth, genders, socioeconomic statuses, disabilities, pregnancy and lactation statuses, and comorbidities. When submitting the plans, clinical study sponsors should include enrollment goals for diverse participation and the rationale for selecting those goals; a plan of action to enroll and retain diverse participants; and the status of meeting enrollment goals throughout the duration of the study.

Narrow eligibility criteria may also limit patient access to clinical studies, which can result in study populations that inadequately reflect real-world patients. Historically, cancer clinical trials have employed restrictive eligibility criteria to define the study population to minimize risk to participants (894). To address this issue, FDA launched Project Pragmatica, which aims to encourage simple cancer clinical studies that incorporate pragmatic design elements, including fewer eligibility criteria. The agency also released three draft guidance

documents in April 2024 that provide recommendations for broadening eligibility criteria to increase participation and diversity in cancer clinical trials (895-897). The draft guidance documents focus on three areas:

- appropriate use of therapeutic washout periods and concomitant medication exclusions;
- laboratory values to describe their appropriate use in determining eligibility to participate; and
- broadening performance status to achieve greater generalizability of results.

FDA continues to demonstrate its commitment to modernizing clinical trials. While some progress has been made, more work is needed holistically to enhance the clinical trial infrastructure. Developing meaningful solutions to increase participation in clinical trials is essential for advancing medical knowledge, improving patient outcomes, and ensuring equitable access to cutting-edge treatments for all individuals affected by cancer.

Rapidly Delivering Safe and Effective Therapies to Patients

Thanks to incredible advances in cancer treatment, many patients with common cancer types are living longer and fuller lives following diagnosis. Continued progress against cancer requires researchers to innovate how they measure whether a novel therapy is safe and effective in a timely manner. To this end, there has been an increasing shift from using the gold standard endpoint of overall survival (OS) (see **Sidebar 28**, p. 90), to earlier endpoints like progression free survival, overall response rate, and duration of response to achieve an accelerated approval designation from FDA. As one example, at a recent Oncologic Drugs Advisory Committee of FDA, the committee unanimously voted in favor of using minimal residual disease (MRD) negativity as an early endpoint to support accelerated approval for multiple myeloma (898).

Unfortunately, early endpoints do not always correlate with OS, which causes uncertainty about the benefit of new drugs (899). To help advance novel early endpoints and improve the quality of benefit-risk analyses, FDA launched Project Endpoint in 2022. A recent article related to Project Endpoint detailed many considerations and new statistical methods to improve the use of limited OS data to evaluate for indications of harm (900). Most importantly, the article encourages trial sponsors to plan ahead to collect and analyze all OS data for every late-stage trial.

One likely cause of the discrepancy between early endpoints and OS is that a new drug may be effective at shrinking a tumor but may also cause severe and delayed toxicities. Traditionally, doses of a cancer drug were determined by escalating the dose until the highest dose of the drug with acceptable side effects, called the maximum tolerated dose, was found. In the era of precision medicine and immunotherapies, increasing doses may not result in better efficacy, but often results in worse side effects (901). To encourage selection of optimal doses of new drugs, FDA issued a draft guidance, titled *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases,* in January 2023 (902). Additionally, two FDA-AACR workshops in 2024—Optimizing Dosages for Oncology Drug Products and How Much Is Enough? Trial Designs for Treatment Regimens with Multiple Phases—convened experts from academia, industry, government, and patient organizations to discuss improving dosage selection (903,904).

Addressing Cancer Drug Shortages

Many cancer drugs are in short supply, and there has recently been momentum to address cancer drug shortages (905). FDA plays a crucial role in addressing and managing drug shortages, including those affecting cancer treatments. Despite the agency's efforts, cancer drug shortages have reached a record high with approximately 16 commonly used cancer drugs in limited supply (906). Increased demand and limited supply along with manufacturing capacity and market dynamics are among the major factors contributing to cancer drug shortages (907). Ten percent of people living with cancer have been adversely impacted by the shortage, with the majority citing treatment delays and difficulty finding alternative therapies (908). FDA continually provides updated drug shortage information and is working closely with drug manufacturers to reduce the impact of shortages, mitigate supply disruption and develop preventative methods to avoid cancer drug shortages (909). The agency's efforts have increased the US supply of cisplatin, a widely used cancer chemotherapeutic, to approximately its pre-shortage levels (910).

In addition to FDA's work, the US Senate Finance Committee proposed a voluntary Medicare Drug Shortage Prevention and Mitigation Program in May 2024 that aims to encourage transparent purchasing practices across supply-chains and drug manufacturers (911). The Centers for Medicare & Medicaid Services (CMS) has also proposed and implemented several policies to help address drug shortages (see **Sidebar 49**, p. 162). Addressing cancer drug shortages remains a critical issue that will require a multifaceted approach involving health care providers, pharmaceutical companies, policymakers, and regulatory bodies to develop and implement solutions that can restore the limited supply of cancer therapies.

SIDEBAR 49

CMS Proposed Policies to Address Drug Shortages

IPPS payment

Centers for Medicare & Medicaid Services (CMS) issued the fiscal year (FY) 2025 Medicare hospital inpatient prospective payment system (IPPS), which includes a separate payment for small, independent hospitals to establish and maintain a buffer stock of essential medicines to use during shortages (912).

Medicare prescription drug inflation rebate program

CMS has issued revised guidance which includes provisions that aim to minimize incentives for drug companies to stay on a shortage list and reduce supply chain disruptions (913).

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. 43). Research has shown that routine screening using evidence-based approaches to detect common cancers and cancer warning signs is essential for improving treatment options and chances of survival (see **Screening for Early Detection**, p. 63). However, inequities in access to screenings and follow-up care for numerous populations contribute to delayed diagnoses and lower chances of survival. Innovative investments in inclusive screening practices, from both health care providers and policymakers, are necessary to improve overall prevention and survival rates. Further expansion of health insurance through Medicaid expansion and growth of the Patient Care and Affordable Care Act (ACA) marketplace plans will also improve access to cancer screening and preventive services.

Human papillomavirus (HPV) can cause several cancers, including nearly all cases of cervical cancer (see **Prevent and Eliminate Infection From Cancer-causing Pathogens**, p. 54). There are effective strategies to prevent HPV infection and its associated cancers, including HPV vaccination, timely screening, and follow-up care. HPV vaccination rates have increased among adolescents, though there is still more to be done to reach the Healthy People 2030 goal of an 80 percent vaccination rate among adolescents (914). In May 2024, FDA approved the use of cervical self-sampling by patients, an important step in expanding access to cervical cancer screening (915).

For health care providers, addressing the needs of patients in rural areas, where screening rates are lower than in urban environments (916), can require adapting to the limitations faced by these populations. Having lower insurance rates, increased distance from health care centers, and lack of public transportation options are all factors faced by women in these areas, resulting in lower breast, cervical, and colorectal cancer screenings (917). However, tools like simultaneous screenings and increased patient navigation services are one way to increase cancer screening for rural populations (917).

CDC Screening Programs

The Centers for Disease Control and Prevention (CDC) is a key federal public health agency that works to increase access to cancer screenings; both CDC programs and CDC-sponsored external organizations work to address cancer screening disparities. Continued investments in programs like CDC's NBCCEDP and support for bills like S.1840 - Screening for Communities to Receive Early and Equitable Needed Services for Cancer Act of 2023, introduced by Senator Collins (R-ME) and Senator Baldwin (D-WI) (918), are necessary tools to increase overall screening rates.

NBCCEDP also does targeted outreach to medically underserved populations, including creating flyers about breast cancer screening for Amish populations and caregiver kits and modified booklets for women with learning disabilities (919). CDC has also created educational materials for populations with a higher rate of breast cancer. This includes the Bring Your Brave campaign, informing Ashkenazi Jewish women about their increased risk of breast cancer due to a higher prevalence of *BRCA* gene mutations in this population (920).

EPA Cancer Moonshot Programs

Agencies like EPA work to assess exposures to carcinogens in the environment and to reduce cancer risks. Within EPA, offices like the Office of Air and Radiation (OAR) create policies that reduce exposure to cancer-causing pollutants (921). Initiatives like the Clean School Bus Program (922) that have allocated funds to replace school buses with zero-emission and low-emission updated models, are not only saving funds with reduced fuel costs, but also lowering

overall pollutant emission exposures in children. EPA is also responsible for emergency responses to hazardous events, including oil spills, radiologic releases, and large-scale national emergencies (923). Work by the agency to keep cancer-causing agents, like arsenic, benzene, perchloroethylene (PCE), and trichloroethylene (TCE) out of public land and drinking water is essential for overall public health and reduction of cancer rates (921).

According to a recent estimate, **5 million Americans** would **stop smoking** within one year **if nicotine content** in cigarettes **is restricted** to minimally addictive levels.

Source: (934).

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Leveraging Policy to Reduce Tobacco-related Illness

Effective tobacco control policies and awareness campaigns have led to historically low smoking rates in the United States. In 2021, 18.7 percent of US adults regularly used any tobacco product (49), and 11.5 percent of adults regularly smoked cigarettes. Progress is also evident with tobacco use among middle and high school students. At the peak of the e-cigarette epidemic in 2019, 31 percent of high school students and 12.5 percent of middle school students regularly used any tobacco product (924). In 2023, those rates were reduced by about half to 12.6 percent and 6.6 percent, respectively, the vast majority of which were illicit flavored e-cigarettes (185). Advancing new tobacco control policies is necessary to continue progress on reducing tobacco-related cancers.

Flavors increase the addictiveness and appeal of tobacco products, particularly for youth. Menthol cigarettes alone were estimated to have caused 378,000 premature deaths in the United States between 1980 and 2018, disproportionately among Black adults (925). In 2022, FDA proposed draft regulations that would prohibit menthol cigarettes and flavored cigars (926). Unfortunately, HHS Secretary Becerra announced these regulations would be delayed for an indefinite time (927). E-cigarettes and other novel tobacco products require proactive authorization from FDA prior to being sold legally in stores. While there are notable examples of fines and seizures of illegal products totaling millions of dollars, these efforts have not yet substantially impacted the multibillion-dollar illicit market (928,929). In June 2024, FDA announced the formation of a new multi-agency task force to improve enforcement against distributors and importers of these illegal products (930).

Additionally, FDA has expressed interest in proposing a regulation to limit nicotine to minimally addictive concentrations in combustible tobacco products (931,932). Several high-quality clinical trials have demonstrated that reducing nicotine levels by 95 percent in cigarettes significantly increases smoking cessation attempts and decreases the number of cigarettes smoked by trial participants (933).

Reducing the addictiveness of tobacco products by prohibiting flavors and minimizing nicotine concentrations would save millions of lives in the coming decades and help achieve the goals of the Cancer Moonshot. Additional policies that could reduce tobacco-related illness include improved insurance coverage of evidence-based smoking cessation therapies; further restrictions on tobacco product advertising and promotions; and increased funding for FDA, NCI, and CDC smoking awareness and cessation programs.

The bipartisan Resources to Prevent Youth Vaping Act (S. 3653) would provide FDA an additional $100 million per year by **collecting user fees from e-cigarette manufacturers** to support critical enforcement efforts.

W51

★ SPOTLIGHT

Accelerating Progress Against Childhood Cancer

From 2015 to 2019, the overall cancer death rate for children ages 0 to 14 years decreased by 1.5 percent per year due to several factors including improved treatments, increased clinical trial participation, and earlier detection (935). However, continued investment in childhood cancer research remains crucial as NCI estimates that 14,910 children and adolescents ages 0 to 19 years will be diagnosed with cancer in 2024 (936).

Childhood cancers are considered "rare diseases," making clinical trials more difficult to complete and limiting the incentive for drug sponsors to invest in approvals for this vulnerable patient population. In some cases, drugs are studied and approved in adults, then data from the trials are extrapolated to determine appropriate usage for childhood cancers. To enhance

incentives for pharmaceutical companies to develop new drugs for childhood cancers, Congress passed the Pediatric Research Equity Act (PREA) in 2003, which authorizes FDA to require studies with children for therapies developed for adults. However, certain exemptions under PREA allowed sponsors to avoid conducting these studies. The Research to Accelerate Cures and Equity (RACE) for Children Act, passed in 2017 and implemented in 2020, was designed to eliminate these exemptions and allow FDA to require sponsors to study the effectiveness of drugs in children when the molecular target of their drug is relevant. Early results from a report by the US Government Accountability Office analyzing the effectiveness of the RACE Act indicate an increased number of planned studies to test certain cancer therapeutics used in adults in children with cancer, though it is still too soon to know if these efforts will result in an increase in drug approval for childhood cancers (937).

Combination therapies have been shown to be incredibly effective in treating many cancers, as they help target the variability of cancer cells in a tumor. Unfortunately, combination therapies were not explicitly outlined in the PREA or the RACE Act. In May 2024, the House Energy & Commerce Health Subcommittee advanced the Give Kids a Chance Act that would authorize FDA to direct companies to study targeted combinations of cancer therapies in pediatric trials, should it become law (938).

Advances in cancer therapy rely on basic scientific understanding, and there is still much to be understood about the underlying mechanisms that lead to childhood cancer. To address this, Congress implemented the Gabriella Miller Kids First Pediatric Research Program (Kids First) in 2015. This program at NIH has two primary initiatives: identifying children with childhood cancer and birth defects, and their families, for whole genome sequencing; and developing a database of clinical and genetic data from patients with childhood cancers to help lead to the discovery of new implicated genetic pathways (939). Gabriella Miller Kids First Research Act 2.0 has been introduced in both the House and the Senate in the 118th Congress, demonstrating continued support for this important initiative. As of June 30, 2024, the bill has passed the House but has not yet passed the Senate.

The Childhood Cancer STAR Reauthorization Act was signed into law in January 2023, reauthorizing the program for an additional 5 years at its fully authorized level of $30 million. This legislation aims to enhance research on the late effects of childhood cancers and establishes a new pilot program to begin to explore innovative models of care for childhood cancer survivors. This reauthorization also supports the Childhood Cancer Data Initiative (CCDI) at $50 million. CCDI is an effort to collect, share, and analyze clinical care and research data on childhood cancers to increase our understanding of childhood cancer and subsequent survivorship. The CCDI has three foundational goals (940):

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

Of note, the Childhood Cancer STAR Reauthorization Act only provides legal authorization for these programs to continue but Congress must fully fund these efforts during the FY 2025 appropriations process.

On April 1, 2023, emergency coverage protections for Medicaid enrollees afforded during the pandemic ended, with the federal government allowing state Medicaid agencies up to 14 months to redetermine the eligibility of enrollees, threatening the coverage of 6.7 million children (941). Earlier this year, CMS released a final rule regarding the simplification of the eligibility and enrollment processes for Medicaid, the Children's Health Insurance Program (CHIP), and the Basic Health Program (BHP) (942). This final regulation simplifies the process for eligible people to enroll and stay enrolled in CHIP coverage, keeping eligible individuals, including children, covered and ensuring equitable access to coverage.

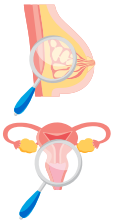
Addressing Cancer Disparities and Improving Patient Outcomes

As described in the *AACR Cancer Disparities Progress Report 2024* (29), cancer and other health disparities are driven by a complex set of interrelated causes, including social, economic, and environmental factors; collectively, these factors are called social determinants or social drivers of health (SDOH) (see **Figure 3**, p. 21) (39,40). Policies that were designed to

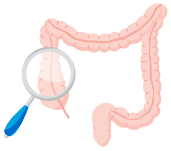
SIDEBAR 50

CDC Programs to Promote Cancer Health Equity

Racial and Ethnic Approaches to Community Health (REACH) is a national program that demonstrates how local and culturally tailored solutions can be effective in reversing the health disparities of diverse communities in urban, tribal, and rural areas. REACH funds community programs that encourage preventive behaviors foundational to cancer prevention, such as physical activity, obesity reduction, healthy eating, smoking cessation, and cancer screening.



The National Breast and Cervical Cancer Early Detection Program, since its inception in 1991, has helped low-income, uninsured, and underinsured women gain access to screening, diagnostic, and treatment services. In 2022, it provided breast cancer screening and diagnostic services to 270,355 women and diagnosed 2,122 invasive breast cancers and 676 premalignant breast lesions. This program also provided cervical cancer screening and diagnostic services to 126,416 women and diagnosed 89 invasive cervical cancers and 5,951 premalignant cervical lesions, of which 34 percent were high-grade.



The Colorectal Cancer Control Program was established in 2015 to increase colorectal cancer screening rates. The program currently constitutes 541 clinics, including those where fewer than 60 percent of patients are up to date. Clinics that have participated since the program's inception have increased screening rates by 8.3 percent.

discriminate against racial and ethnic minority communities, commonly known as systemic or structural racism, continue to produce and reinforce the negative impact of SDOH, and in turn, exacerbate cancer disparities and other health, economic, and social disparities (29). 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.

At the federal level, agencies across the government have diverse programs seeking to further understand and improve health equity. For example, the National Institute on Minority Health and Health Disparities (NIMHD) within NIH is furthering health equity research and practice, including efforts to reduce cancer disparities (943). The CCHE within NCI also has a significant portfolio of programs to conduct research on cancer disparities, broaden opportunities for scientific training, and pilot new initiatives to improve cancer screening (944).

CDC, as the nation's frontline public health agency, has many cancer prevention programs, including efforts to reduce cancer disparities. The CDC's Division of Cancer Prevention and Control provides funding and partners with state and local governments and other organizations to broaden access to screening and other health care services. These actions include the use of tools like mobile mammography vans at worksites and culturally tailored care (839,945,946). CDC has launched its CORE Commitment to Health Equity, managed by the CDC Office of Health Equity, a strategic framework for collaboration across multiple sectors to improve public health for all populations and reduce health disparities (947) (see **Sidebar 50**, p. 165).

Achieving health equity and eliminating cancer disparities will also require policy interventions beyond medical and public health programs. Many of the structural changes proposed in the Health Equity for All Act (HEAA), including expansion of Medicaid coverage, would facilitate access to care for underserved populations across the United States (948). Expanding insurance coverage for cancer-related services, including coverage for comprehensive tobacco cessation programs, is critical. The White House recently announced steps to expand coverage for cancer patient navigation services (949).

Inflation Reduction Act

Policymakers recognize the vital role health systems have in supporting vulnerable populations and have introduced several pieces of legislation seeking to protect innovation for these groups. On August 16, 2022, President Biden signed the Inflation Reduction Act into law – a significant piece of legislation that aims to reduce the federal government budget deficit, lower prescription drug prices, and invest in domestic energy production while promoting clean energy.

Patients with cancer are currently benefiting from specific provisions in the law, most notably the cap that is now in place on out-of-pocket prescription drug costs for older adults. Medicare beneficiaries are receiving better financial protection through this provision that is capping out-of-pocket costs for prescription drugs at $2,000 annually. Additionally, the law is making health coverage more affordable for 13 million people because it extends enhanced ACA marketplace subsidies through 2025.

However, with all major legislation, Congress has a responsibility to continually examine the provisions and identify areas where adjustments are needed. One such example involves the Optimizing Research Progress Hope and New (ORPHAN) Cures Act, which is a proposed bill that would amend the Inflation Reduction Act to ensure medicines that treat one or more rare diseases are excluded from Medicare price negotiations. The bipartisan legislation aims to safeguard existing incentives and advance the development of innovative therapies for the 30 million Americans affected by rare diseases, including 200,000 people living with a rare form of cancer.

Currently, under the Inflation Reduction Act, only orphan drugs that treat a single rare disease would be excluded from price negotiation. The provision could unintentionally discourage manufacturers from seeking additional indications, limiting treatment options for people with rare diseases. About one in five FDA-approve orphan drugs are also approved to treat additional diseases.

Exempting rare disease treatments with multiple approved uses from price negotiation, on the other hand, can help encourage manufacturers to continue investing in groundbreaking treatments for people living with rare diseases.

Environmental Racism and Environmental Justice

Environmental racism can be defined as environmental harm inflicted due to systemic racism (950). Conversely, environmental justice refers to efforts to ensure that populations are not subjected to disproportionate environmental harms, and that all people have equitable access to a sustainable and healthy environment. Racial and ethnic minorities have unjustly been disproportionately harmed by pollutants, including carcinogens (951,952). A glaring example of this is an 85-mile stretch of the Mississippi River from Baton Rouge to New Orleans known as "Cancer Alley" (953). Roughly 25 percent of the nation's petrochemical production is located in this area, and the region has a larger share of Black residents than state or national averages (954). EPA has called out Louisiana policymakers for neglecting the health needs of Black residents and being complicit in environmental racism (955), and the region has been called a "failure of state and federal authorities to properly regulate the [fossil fuel] industry" (956).

Environmental and grassroot activists, as well as EPA, play important roles in advocating for environmental protection and educating residents about the health ramifications of living near waste zones. EPA has a range of programs focused on environmental justice to help ensure that all people have access to a healthy and sustainable environment and are protected from disproportionate environmental harms (957). For communities living with high air carcinogens, tools like EPA's air monitoring systems (958) provide advocates and government officials with data important for regulatory and legal action against polluters. EPA recently issued stricter air pollution rules on chemical plans to address the severe health threats in locations like Cancer Alley (959), and Congress has proposed comprehensive legislation to holistically expand environmental justice (960).

FDA also has an important role in regulating exposures to carcinogens through its consumer protection activities. In 2022, Congress passed the Modernization of Cosmetics Regulation Act of 2022 (MoCRA). This law expands FDA's existing authorities to regulate cosmetic products, including the power to recall cosmetic products in the event that they cause harm to the public (961).

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 a concomitant need to standardize the collection, security, and dissemination of this information for patients, caregivers, clinicians, and researchers. Although there has been progress in the expansion of electronic health records and telemedicine, especially in the wake of the COVID-19 pandemic, there is much work to be done to maximize the benefits of digital healthcare technologies in oncology (962). 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 (963). There are also significant shortcomings in the collection and systematic organization of different types of relevant patient data, including the patient's race and ethnicity, sexual orientation and gender identity, patient reported outcomes of cancer therapy, and diagnostic results (962,963).

Several policy interventions at the state and federal level (as well as actions by industry and health care providers) could help to advance the use of digital technologies in the treatment and management of cancer, while at the same time safeguarding protected health information. These include new rules and guidelines on data standardization and interoperability, the security and privacy of digital health data, new funding/reimbursement mechanisms for digital health technologies, and efforts to reduce bias and promote equity in data collection (962). The federal government has begun to take steps along these lines, for example, issuing new CMS rules on digital health care information interoperability, patient access, and security (964,965).

Conclusion

Since 2011, the annual American Association for Cancer Research (AACR) Cancer Progress Report has captured the incredible advances against cancer, and disseminated this knowledge to the American public, policymakers, and the scientific community. As highlighted in the 14 editions of the report, countless patients with cancer have benefited from the breathtaking pace of progress against cancer. One measure of this progress is 4.1 million cancer deaths averted between 1991 and 2021. To maintain and accelerate this momentum, researchers are continually leveraging scientific discoveries and technological innovations to deliver lifesaving therapeutics for patients with cancer.

The unprecedented advances against cancer documented in the *AACR Cancer Progress Report 2024* and the prior editions stem from the dedicated work of numerous individuals, cancer-focused organizations, and government agencies across the cancer care continuum and can be attributed to the bipartisan and steadfast support of Congress. Among the major advances highlighted in this report is the first ever FDA approval of a new type of cellular immunotherapy in which researchers harness immune cells naturally capable of infiltrating tumors to treat patients with advanced melanoma. Overall, between July 1, 2023, and June 30, 2024, the time period covered by the *AACR Cancer Progress Report 2024*, FDA approved 15 new anticancer therapeutics and expanded the use of 15 previously approved anticancer drugs to treat new types of cancer.

The pace of development and approval of novel therapies specifically designed for childhood cancers has accelerated in recent years. These include targeted therapies that home in on the genetic mutations driving cancer growth. As a result, we are witnessing remarkable improvement in the 5-year relative survival rate for children with cancer, which has risen from 58 percent for those diagnosed in the mid-1970s to 85 percent for those diagnosed between 2013 and 2019.

The progress against cancer highlighted in the *AACR Cancer Progress Report 2024* is a testament to the power of interdisciplinary collaborations among all stakeholders deeply committed to improving public health and maintaining our nation's status as a beacon of innovative cancer science and medicine. This collaborative drive also provides the foundation to overcome the many challenges that remain, such as disparities in the burden of cancer and access to care experienced by medically underserved segments of the US population.

The future of cancer science and medicine is promising. The return on US taxpayers' investments in medical research over the past two decades has been astronomical. But the medical research community depends on the unwavering and historically bipartisan congressional support to maintain the momentum of progress against cancer and capture the unprecedented moment ahead of us. Lifting the caps on federal domestic spending and providing robust, sustained, and predictable funding for medical research are critical to maintain the pace of progress against cancer for the benefit of all patients living with the disease.

AACR Call to Action

From FY 2016 to FY 2023, Congress increased NIH funding for eight consecutive fiscal years. These funding increases for medical research enabled scientific progress and contributed to the longer-term decline in cancer mortality in the United States. As of 2021, the overall cancer mortality rate had decreased by 33 percent from its highest level in 1991. In addition to breakthroughs in therapies, these declines can be attributed to improvements in cancer prevention and early detection.

This progress over the last several decades has also included strides against childhood cancers. Thanks to scientific breakthroughs leading to new therapies and other treatment approaches, cancer death rates among children (14 years and younger) and adolescents (15 to 19 years) declined by 70 percent and 63 percent, respectively, between 1970 and 2021. However, there has recently been a troubling increase in the incidence of certain cancers among people under the age of 50, particularly colorectal cancer and cervical cancer. It is vitally important that policymakers continue to support research and health programs to make progress against all cancers, including those afflicting younger people.

Further action is also needed to address the use of tobacco products. While the percentage of US adults who use combustible tobacco products has declined significantly, cigarette smoking remains the leading preventable cause of cancer in the United States, associated with the development of not only lung cancer but 17 other cancer types. Additionally, many American youth and young adults use electronic cigarettes. Electronic cigarettes still emit many harmful chemicals with unknown long-term health impacts, and there is a large domestic market of illicit flavored e-cigarettes. These challenges will require policymakers to continue to support smoking prevention and cessation initiatives and programs to reduce the use of e-cigarettes.

Additionally, federal investments in medical research must continue to focus on reducing health inequities. Stronger investments in programs at agencies including NIH, NCI, and FDA can boost diversity in the cancer research workforce and enhance clinical trial diversity. Furthermore, higher appropriations for cancer programs at CDC can improve health equity by improving the availability of cancer screening and prevention programs across diverse communities.

A new generation of therapies, including novel immunotherapeutics, antibody-drug conjugates, combination therapies, cell therapies, and proteolysis targeting chimera technology, has already begun to transform cancer treatment. However, strong federal investments in medical research, including through the newly created Advanced Research Projects Agency for Health (ARPA-H), are essential for discovering these treatments as well as to ensure that they become readily available to all patients.

After years of growing federal budgets for medical science, Congress cut NIH funding in FY 2024. This unfortunate outcome was a direct consequence of the Fiscal Responsibility Act (FRA), legislation that passed last year to mandate spending caps for FY2024 and FY2025 to resolve the nation's debt ceiling issue, at least temporarily. The budget reduction that NIH absorbed in FY2024 threatens to curtail the medical progress seen in recent years and stymie future advancements.

While the spending caps remain in place as Congress negotiates its FY 2025 appropriations bills, we are encouraged by the efforts from Senate Appropriations Committee Chair Patty Murray (D-WA) and Senate Appropriations Committee Ranking Member and Vice Chair Susan Collins (R-ME), as well as Senators Tammy Baldwin (D-WI) and Shelley Moore Capito (R-WV), who serve as the Chair and Ranking Member, respectively, on the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, to prioritize a robust funding increase for NIH in FY 2025. First, they worked in a bipartisan manner to make available an additional $13.5 billion in emergency funding for nondefense spending accounts in FY 2025, and second, they then allocated a significant amount of that extra funding ($1.8 billion increase) to NIH to ensure that our nation's leading researchers will have access to the resources that are necessary to make the scientific discoveries that lead to lifesaving cures and improve the health and well-being of people across the nation and around the world.

Therefore, as Congress continues its work on the FY 2025 appropriations bills, AACR urges leaders in the House and Senate to recognize the importance of supporting robust, sustained, and predictable funding growth for the federal medical research and health programs vital to the fight against cancer.

To this end, we call on Congress to:

- **Appropriate at least $51.3 billion in FY 2025 for the base budget of NIH** and at least $7.934 billion for NCI.
- **Provide $3.6 billion in dedicated funding for Cancer Moonshot activities** through FY 2026 in addition to other funding, consistent with the President's FY 2025 budget.

- **Appropriate at least $472.4 million in FY 2025 for the CDC Division of Cancer Prevention** to support comprehensive cancer control, central cancer registries, and screening and awareness programs for specific cancers.
- **Allocate $55 million in funding for the Oncology Center of Excellence at FDA** in FY 2025 to provide regulators with the staff and tools necessary to conduct expedited review of cancer-related medical products.

By following these recommendations, Congress will help accelerate the rate of discovery and create vital pathways for young scientists to contribute to future advances in cancer research. Ultimately, this will improve our nation's health, including the lives of the millions of people who have been affected by cancer.

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Glossary *

Adjuvant therapy Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Advanced Research Projects Agency for Health (ARPA-H) An independent, research funding agency entity within the National Institutes of Health that supports transformative biomedical and health breakthroughs.

Angiogenesis The process of growing new blood vessels from the existing vasculature. Angiogenesis is important for numerous normal body functions, as well as tumor growth and metastasis.

Antibody–drug conjugate A therapeutic comprising an antibody chemically linked to a cytotoxic chemotherapeutic. The antibody binds to specific proteins on the surface of certain types of cells, including cancer cells. The linked cytotoxic chemotherapeutic enters these cells and kills them without harming nearby cells.

Artificial intelligence A phenomenon that leverages computers and machines to mimic the problem-solving and decision-making capabilities of the human mind, such as how to act, reason, and learn.

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

B-cell maturation antigen (BCMA) A receptor that plays an important role in regulating B-cell proliferation and survival. BCMA is expressed on the cell membrane of normal and malignant plasma cells, but not other normal tissues.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Biomedical Research and Development Price Index (BRDPI) A measure of how much the National Institutes of Health budget must change to maintain purchasing power. The BRDPI is updated annually.

Bispecific antibody A type of antibody that can bind to two different antigens at the same time. Bispecific antibodies are being studied in the imaging and treatment of cancer. They are made in the laboratory.

BRCA1/2 Genes that produce proteins that are involved in repairing damaged DNA. Females who inherit certain mutations in a *BRCA1* or *BRCA2* gene are at increased risk of developing breast cancer, ovarian cancer, and some other types of cancer. Males who inherit certain BRCA1 or BRCA2 mutations are at increased risk of developing breast cancer, prostate cancer, and some other types of cancer.

Breast cancer Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

Cachexia Loss of body weight and muscle mass, and weakness that may occur in patients with cancer, AIDS, or other chronic diseases.

Cancer A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinomas begin in the skin or in tissues that line or cover internal organs. Sarcomas begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemias arise in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the blood. Lymphomas and multiple myeloma originate in the cells of the immune system. Central nervous system cancers arise in the tissues of the brain and spinal cord. Also called malignancy.

Carcinogen Any substance that causes cancer.

Carcinoma A cancer that begins in the skin or in tissues that line or cover internal organs.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2024*. NCI has been used as the primary source for most definitions.

Caregiver A person who gives care to people who need help taking care of themselves. Examples include children, the elderly, or patients who have chronic illnesses or are disabled. Caregivers may be health professionals, family members, friends, social workers, or members of the clergy. They may give care at home or in a hospital or other health care setting.

Centers for Disease Control and Prevention (CDC) A federal agency, within the U.S. Public Health Service of the Department of Health and Human Services, whose mission is to protect public health by preventing and controlling disease, injury, and disability. The CDC promotes healthy behaviors and safe, healthy environments. It keeps track of health trends, tries to find the cause of health problems and outbreaks of disease, and responds to new public health threats.

Cervical cancer Cancer that arises in the cervix (the area where the uterus connects to the vagina). The two main types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are caused by persistent infection with certain strains of human papillomavirus (HPV). Normal cells of the cervix do not suddenly become cancerous; they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

Chemotherapy The use of chemical substances to kill or slow the growth of cancer cells.

Chimeric antigen receptor (CAR) A receptor created in the laboratory that is designed to bind to certain proteins on cancer cells. It is then added to immune cells called T cells taken from cancer patients. This helps the T cells find and kill cancer cells that have a specific protein that the CAR is designed to bind to.

Chromosome Structure within the nucleus of a cell that contains genetic information (DNA) and its associated proteins. Except for sperm and eggs, nearly all nondiseased human cells contain 46 chromosomes.

Chronic myelogenous leukemia (CML) A slow-growing cancer in which too many myeloblasts—a type of immature blood cell that makes white blood cells called myeloid cells—are found in the blood and bone marrow. CML is usually marked by a chromosome change called the Philadelphia chromosome, in which a piece of chromosome 9 and a piece of chromosome 22 break off and trade places with each other. Also called chronic granulocytic leukemia and chronic myeloid leukemia.

Circadian rhythm The natural cycle of physical, mental, and behavior changes that the body goes through in a 24-hour cycle. Circadian rhythms are mostly affected by light and darkness and are controlled by a small area in the middle of the brain. They can affect sleep, body temperature, hormones, appetite, and other body functions.

Click chemistry Describes a method of joining molecules together by using simple, practical chemical reactions to synthesize drug-like molecules or create scientific assays.

Clinical trial A type of research study that tests how well new medical approaches work in people. These studies test new methods for screening, preventing, diagnosing, or treating a disease. Also called clinical study.

Colonoscopy Examination of the inside of the colon using a colonoscope that is inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Colorectal cancer Cancer that forms in the colon or the rectum. More than 95 percent of colorectal cancers are adenocarcinomas that arise in cells forming glands that make mucus to lubricate the inside of the colon and rectum. Before a colorectal cancer develops, a growth of tissue or tumor usually begins as a noncancerous polyp on the inner lining of the colon or rectum. Polyps can be found—for example, through colonoscopy—and removed before they turn into cancer.

Computed tomography (CT) A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an X-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

COVID-19 A highly contagious respiratory disease that is caused by the SARS-CoV-2 virus.

Cytokine A type of protein that is made by certain immune and 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 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.

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

Diabetes A disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in elevated levels of glucose in the blood and urine.

Disability-adjusted life years (DALYs) The measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death.

DNA mismatch repair DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage.

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

Endocrine therapy Treatment that adds, blocks, or removes hormones. For certain conditions (such as diabetes or menopause), hormones are given to adjust low hormone levels. Hormones can also cause certain cancers (such as prostate and breast cancer) to grow. To slow or stop the growth of cancer, synthetic hormones or other drugs may be given to block the body's natural hormones, or surgery is used to remove the gland that makes a certain hormone.

Epidermal growth factor receptor (EGFR) A protein found on the surface of some cells to which epidermal growth factor binds, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including many types of lung cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called ErbB1 and HER1.

Epigenetic mark A chemical modification of DNA and/or histones that can control the accessibility of genes. The collection of epigenetic marks across the entire genome is referred to as the epigenome.

Epigenetics The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Extrachromosomal DNA (ecDNA) A double stranded DNA molecule found in various organisms, including humans, that is separate from chromosomes and can be located either inside or outside of the nucleus of a cell. ecDNA can play roles in certain diseases including cancer.

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.

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA and most genes contain the information for making a specific protein.

Genetic testing A laboratory method that looks for changes in genes, gene expression, or chromosomes in cells or tissue of a person. These changes may be a sign of a disease or condition, such as cancer. They may also be a sign that a person has an increased risk of developing a specific disease or condition or of having a child or other family member with the disease or condition. Genetic testing may also be done on tumor tissue to help diagnose cancer, plan treatment, or find out how well treatment is working.

Germline mutation A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Also called germline variant.

Glioblastoma A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord.

Glioma A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

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.

Health-related quality of life (HRQOL) An individual's or a group's perceived physical and mental health over time.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma A cancer of the immune system that starts in white blood cells called lymphocytes.

Hormone One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human development index A summary measure of average achievement in key dimensions of human development including lifespan, health span, knowledge accumulation, and having a quality standard of living.

Human 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 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.

Inflammatory myofibroblastic tumors (IMT) A rare type of cancer that is made up of smooth muscle cells, connective tissue cells, and certain types of immune cells. It can occur anywhere in the body, but it usually occurs in the lung, abdomen, pelvis, or back of the abdomen. Inflammatory myofibroblastic tumors usually occur in children and young adults. They are a type of soft tissue sarcoma.

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 definition for lymphatic system.

Lymphatic system The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body. Also called lymph system.

Lymphocyte-activation gene 3 (LAG-3) A cell surface molecule with diverse biologic effects on T cell function. LAG3 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 lymphoma, 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 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.

Multicancer detection (MCD) assays A type of blood test that is being studied as a way to screen for many types of cancer at the same time. Multi-cancer detection tests work by measuring biomarkers, such as pieces of DNA, that cancer cells release into the blood as they die. These tests may help find cancer in parts of the body that are not easily accessible for physical exam or biopsy.

Multiple myeloma A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

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 United States 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.

Non-Hodgkin lymphoma A term for a large group of cancers that arise in B cells or T cells. Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Cutaneous T-cell lymphoma is one example of a T-cell non-Hodgkin lymphoma.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

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 referred to as an infectious agent.

Patient navigator A person who helps guide a patient through the health care system. This includes help going through the screening, diagnosis, treatment, and follow-up of a medical condition, such as cancer. A patient navigator helps patients communicate with their health care providers, so they get the information they need to make decisions about their health care. Patient navigators may also help patients set up appointments for doctor visits and medical tests and get financial, legal, and social support. They may also work with insurance companies, employers, case managers, lawyers, and others who may have an effect on a patient's health care needs. Also called patient advocate.

Patient reported outcome (PRO) Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

Precision medicine In oncology, precision medicine refers to the tailoring of treatments to the individual characteristics—in particular, the genetics—of patients and their cancer.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells. When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD-1 acts as an immune checkpoint protein or brake.

Programmed death-ligand 1 (PD-L1) A protein on the surface of many cell types, including some tumor cells. When it attaches to PD-1 on the surface of T cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively.

Prostate cancer Cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Prostate-specific membrane antigen (PSMA) A protein that is usually found on the surface of normal prostate cells but is found in higher amounts on prostate cancer cells. PSMA may be used as a target in imaging to help find prostate cancer cells, especially those that may have come back or spread to other parts of the body.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Psycho-oncology An interdisciplinary field to address the physical, psychological, social, and behavioral aspects of the cancer experience for both patients and caregivers.

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 Also called radioisotope, a radionuclide is an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. In cancer medicine, radionuclides are used in diagnostic tests to detect the spread of cancer using imaging as well as in therapeutics, called radiopharmaceuticals, to treat cancer.

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Renal cell carcinoma The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

Ribonucleic acid (RNA) RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins.

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 determinants of health The social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and grow older that can affect their health, well-being, and quality of life. These include economic policies and systems, development agendas, social norms, social policies, and political systems.

Sociodemographic index A number from 0 to 1 that identifies where countries or geographic areas sit on the spectrum of development. It combines rankings of per capita income, average education attainment, and fertility rates.

Somatic mutation An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. Also known as acquired mutations.

Spatial transcriptomics A technique to count the number of transcripts of a gene at distinct spatial locations in a cell or tissue which can be used to assign cell types to specific locations within a sample.

Splicing Process that involves the removal or "splicing out" of certain sequences referred to as intervening sequences, or introns. The final mRNA consists of the remaining sequences, called exons, which are connected to one another through the splicing process.

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 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.

US 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.

US 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.

Uveal melanoma A rare cancer that begins in the cells that make the dark-colored pigment, called melanin, in the uvea or uveal tract of the eye.

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 technology Any technology designed to be used while worn in close contact to the skin, and able to detect, analyze, and transmit information to the wearer and other designated individuals.

Appendix

SUPPLEMENTARY TABLE 1

Newly FDA-approved Anticancer Agents: July 2023–June 2024

TYPE OF TREATMENT	GENERIC NAME	TRADE NAME	WHAT IS IT?	APPROVED FOR?	CLINICAL TRIAL(S)	ADMINISTERED AS
Surgery Chemotherapy Radiotherapy	pegulicianine	Lumisight	Imaging agent	Certain type of breast cancer	NCT03686215	Injection
	melphalan	Hepzato kit	Chemotherapeutic	Uveal melanoma that has metastasized to liver*	NCT02678572	Injection
Molecularly Targeted Therapy	adagrasib†	Krazati	Cell-signaling inhibitor	Certain type of colorectal cancer*	NCT03785249	Tablet/Capsule
	belzutifan	Welireg	Cell-signaling inhibitor	Certain type of kidney cancer*	NCT04195750	Tablet/Capsule
	capivasertib and fulvestrant†	Truqap and Faslodex	Cell-signaling inhibitor	Certain type of breast cancer	NCT04305496	Tablet/Capsule + Injection
	eflornithine	Iwilfin	Cell-signaling inhibitor	Certain type of neuroblastoma*	NCT02395666	Tablet/Capsule
	encorafenib with binimetinib†	Braftovi and Mektovi	Cell-signaling inhibitor	Certain type of lung cancer*	NCT03915951	Tablet/Capsule
	fam-trastuzumab deruxtecan-nxki†	Enhertu	Antibody-drug conjugate	HER2-positive solid tumors*	NCT04482309 NCT03505710 NCT04744831	Injection
	fruquintinib	Fruzaqla	Angiogenesis inhibitor	Certain type of colorectal cancer*	NCT04322539 NCT02314819 NCT04322539	Tablet/Capsule
	imetelstat	Rytelo	DNA repair inhibitor	Myelodysplastic syndromes	NCT02598661	Injection
	ivosidenib†	Tibsovo	Epigenome-modifying agent	Myelodysplastic syndromes*	NCT02074839	Tablet/Capsule
	momelotinib	Ojjaara	Cell-signaling inhibitor	Myelofibrosis	"NCT04173494 NCT01969838"	Tablet/Capsule
	niraparib and abiraterone acetate†	Akeega	DNA repair inhibitor	Certain type of prostate cancer*	NCT03748641	Tablet/Capsule
	nirogacestat	Ogsiveo	Cell-signaling inhibitor	Desmoid tumors	NCT03785964	Tablet/Capsule
	pirtobrutinib	Jaypirca	Cell-signaling inhibitor	Certain types of lymphoma*	NCT03740529	Tablet/Capsule
	quizartinib†	Vanflyta	Cell-signaling inhibitor	Certain type of leukemia	NCT02668653	Tablet/Capsule
	repotrectinib	Augtyro	Cell-signaling inhibitor	NTRK-positive solid tumors and certain lung cancers	NCT03093116	Tablet/Capsule
	tovorafenib	Ojemda	Cell-signaling inhibitor	Certain type of glioma	NCT04775485	Tablet/Capsule
	zanubrutinib	Brukinsa	Cell-signaling inhibitor	Certain types of lymphoma*	NCT03332017	Tablet/Capsule
Immunotherapy	durvalumab	Imfinzi	Immune checkpoint inhibitor	Certain type of endometrial cancer*	NCT04269200	Injection
	elranatamab-bcmm	Elrexfio	Bispecific antibody	Multiple myeloma	NCT04649359	Injection
	epcoritamab-bysp	Epkinly	Bispecific antibody	Certain type of lymphoma*	NCT03625037	Injection
	lifileucel	Amtagvi	Tumor infiltrating lymphocyte	Melanoma	NCT02360579 NCT03083873 NCT03108495 NCT03645928 NCT04614103"	Injection
	lisocabtagene maraleucel	Breyanzi	CAR T-cell therapy	Certain types of lymphoma*	NCT02631044	Injection
	nogapendekin alfa inbakicept-pmln	Anktiva	Immune system modifier	Certain type of bladder cancer	NCT0302285	Injection
	pembrolizumab	Keytruda	Immune checkpoint inhibitor	Biliary tract cancer*	NCT04003636	Injection
	talquetamab-tgvs	Talvey	Bispecific antibody	Multiple myeloma	NCT03399799	Injection
	tarlatamab-dlle	Imdelltra	Bispecific antibody	Certain type of lung cancer	NCT05060016	Injection
	tislelizumab-jsgr	Tevimbra	Immune checkpoint inhibitor	Certain type of esophageal cancer	NCT03430843	Injection
	toripalimab-tpzi	Loqtorz	Immune checkpoint inhibitor	Nasopharyngeal carcinoma	NCT03581786	Injection

* New cancer type approved 2023–2024.

† Requires a companion diagnostic.

Listed are the new anticancer therapeutics approved by FDA and previously approved anticancer therapeutics that were approved by FDA for treating additional types of cancer.

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AACR Initiatives Accelerating Cancer Research

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Mission

The mission of the AACR is to prevent and cure cancer through research, education, communication, collaboration, science policy and advocacy, and funding for cancer research. Through its programs and services, AACR fosters research in cancer and related biomedical science; accelerates the dissemination of new research findings among scientists and others dedicated to the conquest of cancer; promotes science education and training; and advances the understanding of cancer etiology, prevention, diagnosis, and treatment throughout the world.

Membership

- AACR has more than 58,000 members residing in 142 countries and territories around the world.
- Presently, 32% of members live outside the United States and 22% of AACR's international members are located in countries with emerging economies.
- Members include laboratory, translational, and clinical researchers; other health care professionals; and cancer advocates who depend on AACR's programs and activities for the exchange of timely scientific information.
- With over 31,000 Associate members, AACR supports the education, training, and professional development of early-career cancer researchers/scientists, who are graduate students, medical students and residents, and clinical and postdoctoral fellows. Annual dues are not required for Associate members.
- Through the Diversity, Equity, and Inclusion efforts of AACR-Minorities in Cancer Research and AACR Women in Cancer Research, AACR supports the professional development and career advancement of underrepresented minority and women scientists in cancer research.
- Open to any AACR member are Scientific Working Groups to explore expanded research opportunities and advance discoveries that lead to greater knowledge and understanding of cancer.

Publications

The AACR proudly publishes **10 scientific journals** of high quality, covering the full spectrum of cancer science and medicine, including the online-only, open access journal, ***Cancer Research Communications***.

Cancer Today is a magazine for cancer patients and caregivers.

Leading Discoveries is a magazine highlighting AACR members, programs, and philanthropic initiatives.

The **AACR Progress Reports** are a cornerstone of AACR's educational and advocacy efforts. The purpose of Report(s) is to inform Congress and the American public about the unprecedented progress against cancers; underscore the importance of and advocate for federal funding for cancer research; highlight the current challenges; and emphasize the urgent need to address cancer health disparities, with the overarching goal to achieve health equity for all people, regardless of their race, ethnicity, age, gender, sexual orientation, socioeconomic status, or geographic location.

Other AACR publications include the ***AACR Annual Impact Report***;

and the blog ***Cancer Research Catalyst***.

AACR Grants Program

- AACR funds research directly, as well as in cooperation with numerous cancer-focused organizations. As the Scientific Partner of Stand Up To Cancer, AACR provides expert peer-reviewed grant administration and scientific oversight of team science and individual grants for cancer research projects that have the potential to improve patient outcomes.
- Since establishing its grants program in 1993, AACR has provided over $528 million in funding for cancer research projects.

Meetings

AACR hosts more than 30 scientific conferences and educational workshops annually. The largest of these events is the AACR Annual Meeting. The next AACR Annual Meeting will be held April 25-30, 2025, in Chicago, Illinois.

Policy and Advocacy

- The AACR Office of Science Policy and Government Affairs actively communicates with legislators and policymakers about the value of cancer research and related biomedical sciences to reduce cancer-related morbidity and mortality. It also advocates for critical federal cancer research funding.
- The AACR Scientist↔Survivor Program® provides support for cancer survivors and their families

AACR Project GENIE®

AACR Project GENIE® is an open-source, international, pancancer registry of real-world data assembled through data sharing between a cohort of leading international cancer centers. The registry leverages ongoing clinical sequencing efforts at participating cancer centers by pooling their data to serve as an evidence base for the entire cancer community.

AACR Foundation

The AACR Foundation accelerates progress in the conquest of cancer by providing financial support for scientific research, education, and communication. The Foundation funds programs deemed by the AACR to be of the highest priority and impact. Eighty-six cents of every dollar donated goes directly to lifesaving cancer research.

Professional Development

AACR supports education and training of cancer scientists and clinicians and provides professional development opportunities and resources to enhance and advance their careers. AACR CancerCareers.org is one resource that offers unparalleled career services and opportunities to cancer biomedical researchers and to potential employers who seek to recruit them.

AACR 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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