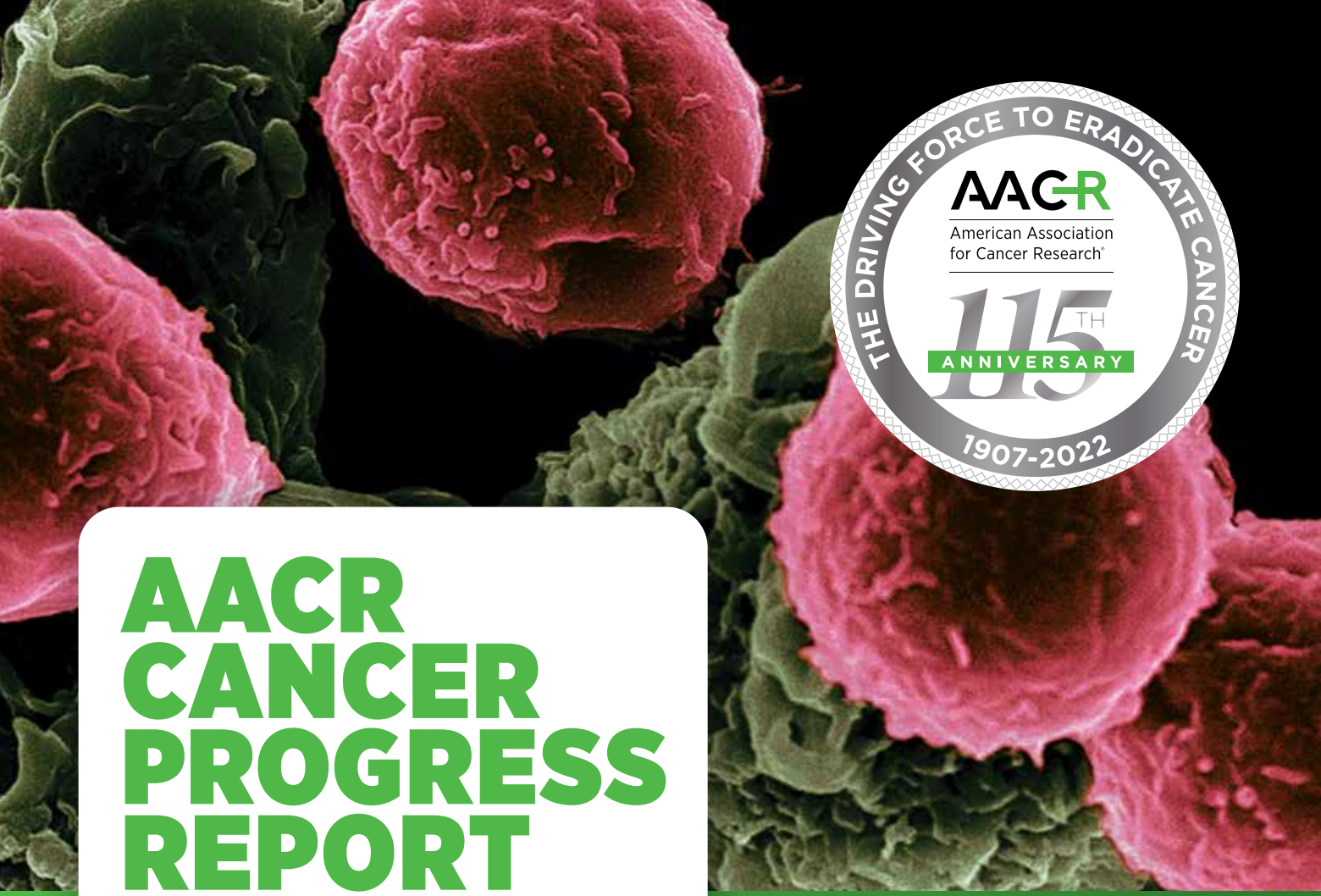

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ABOUT THE
American Association for Cancer Research

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 52,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 130 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting. In addition, the AACR publishes 10 prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policy makers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit **AACR.org**.

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A Message from AACR

We have evidenced unprecedented progress against cancer in the last decade. Remarkable advances across the spectrum of medical research, enabled by decades of federal investments, have led to profound improvements in cancer prevention, detection, diagnosis, and treatment. As a result, the U.S. cancer death rate is steadily declining, and more people than ever before are living longer and fuller lives after a cancer diagnosis. In fact, the number of children and adults living with a history of cancer exceeded a record 18 million in January 2022.

The vital importance of research for improving health and saving lives from cancer is highlighted in this twelfth edition of the annual American Association for Cancer Research (AACR) Cancer Progress Report. As emphasized in the report, federal funding for medical research, supported primarily by investments in the National Institutes of Health (NIH), has enabled researchers to decode the biological complexities of cancer and has accelerated the pace at which this knowledge is being integrated to transform outcomes for patients.

Among the advances detailed in the report are the eight new anticancer therapeutics that were approved by the U.S. Food and Drug Administration (FDA) between August 1, 2021, and July 31, 2022. Several of these groundbreaking therapeutics highlight how researchers are rapidly harnessing the knowledge gleaned from discovery science to transform patient outcomes.

The first ever approval of a molecularly targeted therapeutic against hypoxia-inducible factor-2 alpha for patients with solid tumors associated with von Hippel-Lindau disease, a rare inherited condition characterized by the growth of tumors and cysts, underscores the remarkable progress in our understanding of cancer biology.

It took nearly four decades from the initial discoveries uncovering the molecular underpinnings of chronic myelogenous leukemia in the 1960s to the approval of imatinib, the first BCR-ABL targeted therapeutic against the disease, in the 2000s. Since then, subsequent generations of BCR-ABL targeted therapeutics have been developed rapidly. The most recent approval of the sixth agent, asciminib, with a unique mechanism of action provides new hope for patients with chronic myelogenous leukemia whose cancer has developed resistance against the other available treatments.

Another area of cancer treatment in which extraordinary progress is being made is immunotherapy. One immunotherapeutic was recently approved as the first ever treatment for uveal melanoma, the most common form of eye cancer in adults. The use of immune checkpoint inhibitors (ICI)—therapeutics that work by releasing brakes on natural cancer-fighting immune cells called T cells—is continuing to expand. In 2011, there was only one checkpoint inhibitor approved by FDA. As of July 31, 2022, there are nine checkpoint inhibitors approved by FDA, including the newly approved relatlimab, an inhibitor against the protein LAG-3, a novel immune checkpoint target. Expansion of our knowledge of the immune system and its interactions with other cells within a tumor, catalyzed by interdisciplinary team science and technological innovations, will continue to shape the future of immunotherapy and lead to more breakthroughs for patients.

Despite major advances in our understanding of the disease, cancer continues to pose a significant threat in the United States and worldwide. This is underscored by the sobering reality that in the United States alone, an estimated 600,000 lives will be lost to cancer in 2022. This number is predicted to increase considerably in the coming decades because the segment of the U.S. population that accounts for nearly 60 percent of cancer diagnoses—those age 65 and older—is growing. Individuals with certain underlying comorbidities, such as those living with HIV, are at a higher risk of developing cancer. Thanks to highly effective treatments, more people with HIV are living longer and healthier lives. However, as the population living with HIV continues to age, the epidemiology of HIV-associated cancers is also evolving. It is critical that public health experts implement evidence-based strategies to improve cancer prevention, early detection, diagnosis, treatment, and survivorship for everyone, and particularly for populations that are most vulnerable to cancer such as those living with HIV.

In the United States, effective public education and policy initiatives have contributed to some of the greatest reductions in cancer morbidity and mortality. It is imperative that all stakeholders work together to raise awareness of the cancer risk factors that are potentially modifiable and implement policies to minimize the burden of cancer from these causes.

Cancer can strike anyone—regardless of age, race, ethnicity, ancestry, socioeconomic status, sexual orientation, gender identity, geographic location, or political affiliation. Yet, as highlighted in this report, advances against cancer have not benefited everyone equally; racial and ethnic minorities and certain underserved populations shoulder a disproportionate burden of cancer. This is unacceptable. As a scientific organization focused on preventing and curing all cancers, diversity, equity, and inclusion are at the core of our work. AACR is fiercely committed to understanding and addressing the biological and systemic roots of cancer disparities and to ensuring that health equity through research, policy, and advocacy is a national priority.

As we look to the future, we strongly believe that we have never been in a better position to take lifesaving cancer science from the bench to the clinic. Thanks to bipartisan leadership in Congress that has delivered steady, significant annual funding

increases for NIH, we now have the scientific knowledge, cutting-edge technologies, and capability to deliver unprecedented advances to all cancer patients. However, as we recover from the devastating impact of COVID-19 on cancer research and patient care, ensuring that medical research remains a high priority for our nation's policy makers is vital if we are to maintain the momentum against cancer.

AACR is thrilled that in February 2022, U.S. President Joseph R. Biden, Jr., announced a reignition of the Cancer Moonshot. With the year 2022 marking the 115th anniversary of our existence, AACR and its members are unified in our strong resolve to work alongside the Biden administration toward achieving our shared goal of "ending cancer as we know it today." The reignited Cancer Moonshot will provide an important framework to improve cancer prevention strategies; increase cancer screenings and early detection; reduce cancer disparities; and propel new lifesaving cures for patients with cancer. Therefore, AACR urges Congress to continue to support robust, sustained, and predictable annual increases in the budgets of NIH and NCI, and to provide consistent and sufficient annual funding for the Cancer Moonshot, FDA, and the Centers for Disease Control and Prevention. These actions will transform cancer care, increase survivorship, and bring lifesaving cures to the millions of people whose lives are touched by cancer.

Lisa M. Coussens, MD (hc), PhD, FAACR
AACR President

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

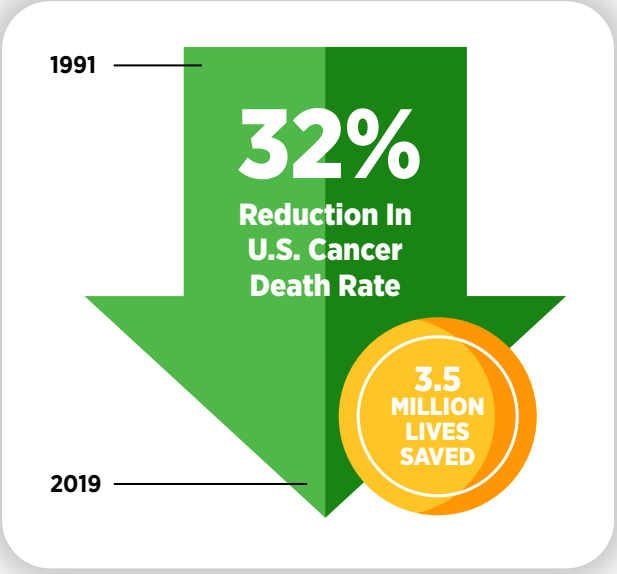
Executive Summary

This is an exciting time in cancer science and medicine. Transformative research and technological innovations are driving unprecedented progress against the collection of diseases we call cancer. As the first and largest professional organization in the world dedicated to advancing all areas of cancer research and patient care, AACR has been and continues to be a catalyst for scientific breakthroughs that save and enhance the lives of cancer patients. It is also committed to increasing public understanding of cancer and advocating for increased federal funding for cancer research and related sciences.

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

Cancer in 2022

The remarkable progress being made against cancer—in particular, improvements in reducing smoking rates and developments in early detection and treatment—is resulting in a steady fall in cancer death rates, and a consistent rise in the number of people who live longer after a cancer diagnosis. In fact, in the United States, the age-adjusted overall cancer death rate has been declining since the 1990s, with the reductions between 1991 and 2019 translating into nearly 3.5 million cancer deaths avoided. Additionally, the number of cancer survivors living in the United States has exceeded 18 million as of January 1, 2022.



Unfortunately, certain U.S. populations, including racial and ethnic minorities and several other medically underserved groups, have not benefited equally from the advances against cancer. Complex and interrelated factors referred to as social determinants of health have contributed to cancer health disparities in the United States. It is imperative that all stakeholders work together to eradicate the systemic and structural injustices that are barriers to health equity.

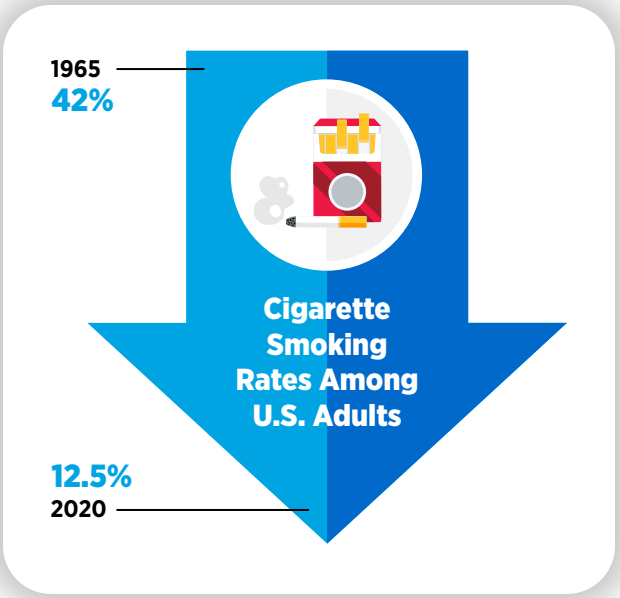
Cancer exacts an immense toll because of the number of lives it affects each year and its significant economic impact. The direct medical costs of cancer care are one measure of the financial impact of cancer, and in the United States alone they were estimated to be $183 billion in 2015, the last year for which these data are currently available; this cost is projected to increase to $246 billion by 2030. The burden of cancer and its economic toll, both on individuals and the U.S. health care system, are expected to rise in the coming decades, highlighting the urgent need for more research to accelerate the pace of progress against cancer.

Understanding How Cancer Develops

Discoveries across the spectrum of cancer research, from basic to translational, clinical, and population science, have led to our current understanding of how cancer develops. We now understand that cancer is a collection of diseases characterized by the inability of a cell to respond to normal biological cues that regulate processes including cell division, identity, and life span. This happens primarily through alterations in the genetic material of normal cells. The identity of genetic alterations and the order and speed at which a cell acquires them determine the length of time it takes a particlular cancer to develop.

Inherited mutations play a role in about 10 percent of cancer cases, but most cancers are caused by mutations acquired over an individual's lifetime. Some mutations are acquired during normal cell division; others are acquired because of persistent exposure to substances that damage genetic material, such as carcinogens in tobacco smoke and ultraviolet (UV) radiation from the sun among other cancer risk factors; and yet other mutations are associated with underlying medical conditions, such as chronic inflammation.

Although genetic alterations underpin cancer initiation and progression in most cases, interactions between cancer cells and their environment, known as the tumor microenvironment, play an important role in disease progression.



Preventing Cancer: Identifying Risk Factors

Decades of research have led to the identification of numerous factors that increase a person's risk of developing cancer. Given that exposure to many of these factors can be eliminated or reduced, many cases of cancer can be prevented. In fact, it is estimated that about 40 percent of cancer cases in the United States are attributable to preventable causes.

The main preventable causes of cancer are tobacco use, obesity, poor diet, lack of physical activity, alcohol consumption, exposure to UV light from the sun or tanning devices, and failure to use interventions that treat or prevent infection with cancer-associated pathogens, such as cancer-causing strains of the human papillomavirus (HPV).

The development and implementation of public education and policy initiatives designed to eliminate or reduce exposure to preventable causes of cancer have reduced cancer incidence, morbidity, and mortality in the United States. Thanks to such initiatives, cigarette smoking rates among U.S. adults have been declining for more than five decades. Unfortunately, the current popularity of electronic cigarettes (e-cigarettes) among U.S. youth and young adults threatens to reverse the significant progress against tobacco use. In addition, the prevalence of obesity, another major risk factor that is linked to 15 types of cancer, continues to rise among U.S. adults and children. These troubling trends have the potential to slow the steady decline in cancer death rates that we have seen in recent years. Therefore, it is essential that all stakeholders work together to enhance the dissemination of our current knowledge of cancer prevention and implement evidence-based policies and programs to minimize the incidence, morbidity, and mortality of cancers attributable to preventable causes.

Screening for Early Detection

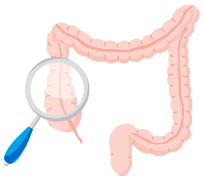
The purpose of cancer screening is to determine whether a person has precancerous lesions or cancer before any signs or symptoms of the disease appear, with the overarching goal of reducing the burden of cancer at the population level. The decision of whether an individual should be screened for cancer is determined by several factors including age; whether or not a person has a particular organ; smoking history; an all-negative prior screening history; life expectancy; family history of cancer; and/or race and ethnicity.

Currently, the U.S. Preventive Services Task Force (USPSTF)—an independent, volunteer panel of national experts in disease prevention and evidence-based medicine—has guidelines for five different types of cancer, four of which apply to individuals who are at an average risk of developing breast, colorectal, prostate, or cervical cancer. Guidelines for lung cancer apply to former or current smokers, i.e., individuals who are at a high risk of developing the disease because of tobacco use.

One area of rapid progress is the use of artificial intelligence (AI)-driven software systems for early detection. As just two examples of the advances in this area, during the 12 months covered by this report, FDA approved Lunit INSIGHT MMG to identify breast lesions suspected of being cancerous, and EndoScreener to identify potentially precancerous polyps during a colonoscopy.

Despite the many benefits, uptake of cancer screening among eligible individuals remains suboptimal. Underuse of routine cancer screening, as well as use of screening tests beyond the recommended age is common. There are also disparities among racial and ethnic minorities and medically underserved U.S. populations in adherence to cancer screening guidelines. Stakeholders across the cancer care continuum are working together to educate the public about the importance of cancer screening and to increase adherence to cancer screening in the general population. Some strategies that have proven effective to achieve this goal include comprehensive public health campaigns; increased access to health insurance; community engagement and culturally tailored interventions; reduced structural barriers; and improved patient–provider communication.

CDC's **Colorectal Cancer Control Program increased colorectal cancer screening rates**, on average, by 8.2 percentage points and 12.3 percentage points for clinics that participated in the program for two years and four years, respectively.



Decoding Cancer Complexity. Integrating Science. Transforming Patient Outcomes.

Researchers are harnessing the knowledge gleaned from the molecular underpinnings of cancer initiation and progression to develop safer and more effective treatments for cancer. Advances in novel and innovative approaches to surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—the five pillars of cancer treatment—are saving and improving lives. From August 1, 2021, to July 31, 2022, FDA has approved two imaging agents and eight new anticancer therapeutics, and has expanded the use of 10 previously approved anticancer therapeutics to treat additional cancer types. Many of the approvals are groundbreaking.

In August 2021, FDA approved belzutifan (Welireg) for adults, such as **Alexandra Vitale** (see p. 76), who have von Hippel-Lindau (VHL) disease, which is a rare and inherited disorder that increases the risk of developing certain types of cancer. In October 2021, FDA approved the molecularly targeted therapeutic, asciminib (Scemblix), to treat patients with chronic myeloid leukemia whose cancer cells carry a specific genetic alteration. In March 2022, FDA approved the first combination of a radiodiagnostic agent and a radiotherapeutic agent to visualize and eradicate prostate cancer.

Another significant leap forward in treating cancers is the approval of an immune checkpoint inhibitor against a novel target, the first such approval in more than eight years. The immunotherapeutic, relatlimab-rmbw (Opdualag), approved in March 2022 to treat melanoma, has already benefited patients, such as **Johnny Borgstrom** (see p. 92), who has been cancer free for more than two years since his treatment. FDA approval in June 2022 of a combination of two molecularly targeted therapeutics—dabrafenib (Tafinlar) and trametinib (Mekinist)—vastly expands the treatment options for adult and pediatric patients, such as **Tyler Richards** (see p. 84), who have a solid tumor harboring a specific genetic alteration.

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.

Supporting Cancer Patients and Survivors

Research-fueled advances in cancer detection, diagnosis, and treatment are helping more people to survive longer and lead fuller lives after a diagnosis of cancer. According to the latest estimates, more than five percent of the U.S. population is living with a history of a cancer diagnosis, equating to more than 18 million people; three out of four U.S. families have at least one member who has experienced a cancer diagnosis. This is in stark contrast to 50 years ago, when cancer survivors constituted only 1.4 percent of the U.S. population. Researchers predict that there will be 26 million survivors in the U.S. by 2040.

A study in 1,500 cancer survivors conducted over a 9-year period found that **survivors who led an active lifestyle had 66 percent lower rates of all-cause mortality** compared to those who led a sedentary lifestyle.

Rapid advances across the continuum of cancer research and patient care have highlighted the current gaps in our knowledge that require additional investigation. We have learned that because of their disease and treatment, survivors of cancer may face serious and persistent adverse outcomes, including physical, emotional, and psychosocial challenges. These challenges can also extend to friends and family members who often act as informal caregivers.

Researchers are exploring ways to utilize health behaviors, palliative care, psycho-oncology, and other evidence-based strategies to improve quality of life for survivors of cancer. As one example, it has been indicated that an active lifestyle can help mitigate the numerous physical, mental, and emotional challenges that survivors of cancer may experience.

Ongoing research is investigating the potential of new technologies and innovative intervention strategies for coordinated care that improves the quality of life and meets the personalized needs of cancer survivors and caregivers from all age groups.

Looking to the Future of Cancer Science and Medicine

Research drives progress against cancers because it provides us with a deeper understanding of cancer biology which leads to advances in prevention, detection, diagnosis, treatment and to the deployment of evidence-based policies for improving public health.

As we look to the future, many researchers, including **AACR President, 2022-2023, Lisa M. Coussens, MD (hc), PhD, FAACR**, (see p. 118), are confident that we can accelerate the pace of progress against cancer by facilitating synergistic collaborations across disciplines and by assembling and supporting a diverse workforce. The new wave of innovation driven by advances in discovery science will enable researchers to gain a greater insight into the mechanisms underlying cancer development, and to identify novel ways to target and eradicate cancer cells. In addition, incorporation of cutting-edge technologies, such as liquid biopsies and AI, will allow us to achieve the full potential of precision medicine by addressing a wide range of unresolved clinical questions across the spectrum of cancer research and patient care.

Impacting the Future of Cancer Research and Patient Care Through Evidence-Based Policies

Steady declines in U.S. cancer incidence and mortality during the past three decades have been fueled by scientific discoveries and initiatives supported by federal investments in NIH, NCI, FDA, and CDC. The enormous excitement in cancer science and medicine has led to a surge in the number of grant applications from researchers, but increases to NCI funding levels have not kept pace to support the same level of innovation experienced in the 1990s.

Robust, sustained, and predictable annual budget increases for NIH and NCI are paramount for maintaining the positive momentum against cancer. Congress's ongoing commitment for supporting FDA also helps ensure that anticancer therapeutics continue to be safe and effective. Additionally, federal support for CDC's cancer prevention and control programs helps bring lifesaving preventive services to those who need them the most. Federal investments are vital for diversifying the cancer research and care workforce, advancing regulatory science initiatives, and pursuing policies that improve cancer prevention, early detection, and control for everyone.

AACR Call to Action

Cancer continues to be the second leading cause of death in the United States, thus there is an urgent need for more research to accelerate the pace of progress against this disease that touches so many lives. Remarkable bipartisan, bicameral efforts in Congress have increased NIH funding by $14.9 billion, or roughly 49 percent, from FY 2015 to FY 2022. These significant investments have made it possible for researchers to discover scientific breakthroughs against cancer and many other diseases.

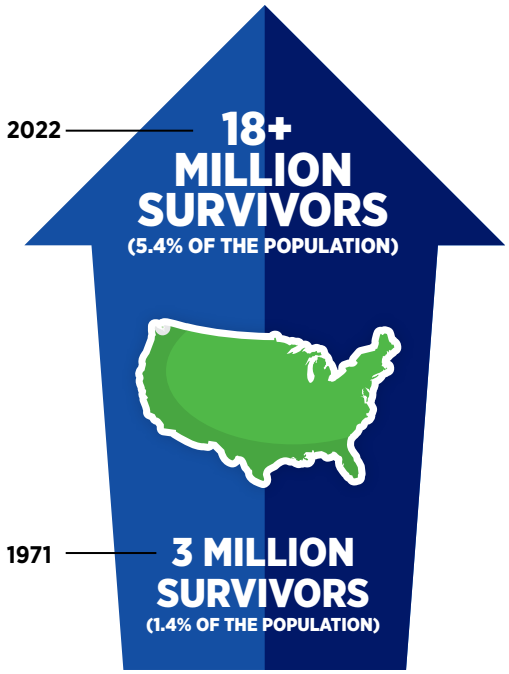
AACR deeply appreciates the commitment of Congress to expediting progress against cancer and other diseases through robust funding increases for NIH, as well as its support of the critical regulatory science work at FDA and public health initiatives at CDC. These investments and initiatives will transform cancer care, increase survivorship, and maintain the United States' position as a global leader in science and cancer research.

Therefore, AACR strongly encourages Congress and stakeholders committed to eradicating cancer to:

- Continue to support robust, sustained, and predictable funding growth for NIH and NCI by providing increases to the FY 2023 base budget, including $49.1 billion in base budget authority for NIH, representing an increase of $4.1 billion, and $7.766 billion for NCI, which is an increase of $853 million and is consistent with the NCI Director's Professional Judgment Budget.
- Fully fund initiatives authorized in the 21st Century Cures Act, including the National Cancer Moonshot, and ensure that Moonshot funding supplements rather than supplants NIH funding in FY 2023.
- Reauthorize the Childhood Cancer STAR Act and provide no less than $30 million for STAR Act implementation, as well as $50 million for the Childhood Cancer Data Initiative, which seeks to better understand cancer biology specific to pediatric patients and improve prevention, treatment, quality of life, and survivorship.
- Invest in vital initiatives of the CDC Division of Cancer Prevention and Control by providing at least $462.6 million to support comprehensive cancer control, central cancer registries, and screening and public awareness programs for specific cancers.
- Increase funding for FDA's critical regulatory science initiatives that advance the development and regulation of oncology products, by providing an increase of at least $318 million, for a total of $3.653 billion in discretionary budget authority in FY 2023, as recommended in President Biden's budget.
- Ensure that patients with cancer have equitable access to quality, affordable health care by expanding Medicaid and enacting the Accelerating Kids' Access to Care Act, which would reduce barriers to care for children on Medicaid who receive specialist care from an out-of-state pediatric provider.
- Increase participation and diversity of cancer clinical trials by reducing barriers for patient enrollment and encouraging diverse representation in clinical trials, as contained in the Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, respectively.
- Encourage research institutions to recruit, support, and retain a robust cancer research workforce that reflects the diversity of our society, and support NCI initiatives such as the NCI Equity and Inclusion Program that strive to build a more inclusive and equitable workforce and markedly reduce cancer disparities.
- Reduce cancer incidence and mortality by addressing nicotine addiction through expanded coverage of tobacco cessation services, removing flavored tobacco products including menthol from the market, and limiting nicotine concentration in tobacco products.
- Expand tax policies to encourage philanthropic giving so that nonprofit cancer research organizations can continue to fund high-risk, high-reward research proposals and accelerate the discovery of new treatments and cures.

The items contained in AACR Call to Action would fuel innovation and usher in a new era of cancer science, reduce cancer disparities, improve cancer prevention and detection, and bring lifesaving cures to millions of people whose lives are touched by cancer.

A Snapshot of a Year of Progress



Between August 1, 2021, and July 31, 2022, FDA approved:

- **8** New anticancer therapeutics
- **10** Previously approved anticancer therapeutics for treating new cancer types
- **2** New diagnostic imaging agents

Researchers continue to combine the power of precision medicine, leading to advances in:

RADIOTHERAPY
The first approval of a radiodiagnostic and a radiotherapeutic agent simultaneously to detect and destroy metastatic prostate cancer cells.

MOLECULARLY TARGETED THERAPY
The first approval of a combination of two molecularly targeted therapeutics to treat any solid tumor with a specific genetic alteration, which is already helping patients such as **Tyler Richards** (see p. 84).

IMMUNOTHERAPY
The approval of a new immune checkpoint inhibitor against a novel target in combination with a previously approved immune checkpoint inhibitor, to treat patients with melanoma, such as **Johnny Borgstrom** (see p. 92).

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

- A new BCR-ABL targeted therapeutic with a novel mechanism of action which provides new hope for patients with chronic myelogenous leukemia whose cancer has developed resistance against the available treatments.
- The first antibody-drug conjugate for treating patients with cervical cancer, such as **Jennifer Myers** (see p. 88).
- The first HIF2α-targeted therapeutic to treat patients, such as **Alexandra Vitale** (see p. 76), with tumors associated with von Hippel-Lindau syndrome.

Research continues to advance immunotherapy, leading to:

- Approval of an immune checkpoint inhibitor to treat any patients with solid tumors whose cancers have a specific genetic biomarker.
- The first bispecific antibody to treat a rare form of melanoma, called uveal melanoma, for which there was no standard of care treatment available.
- A new CAR T-cell therapy to treat patients with multiple myeloma.

Cancer in 2022

IN THIS SECTION YOU WILL LEARN:

- In the United States, the age-adjusted overall cancer death rate has been steadily declining since the 1990s, with the reductions between 1991 and 2019 translating into nearly 3.5 million cancer deaths avoided.
- In the past three years, the number of cancer survivors living in the United States increased by more than a million, reaching greater than 18 million as of January 1, 2022.
- Certain U.S. populations have not benefited equally from the advances against cancer.
- The personal burden of cancer and its economic toll both on individuals and the U.S. health care system are expected to rise in the coming decades, highlighting the urgent need for more research to accelerate the pace of progress against cancer.

Research: Driving Progress Against Cancer

Medical research is the foundation of progress against the collection of many diseases we call cancer. Research improves survival and quality of life for people around the world because it is the driving force behind every advance in cancer science and medicine and every legislative action designed to improve public health. Each breakthrough against cancer is the culmination of a complex, multifaceted process that takes long-term commitment and years of effort by individuals from all segments of the medical research community (see sidebar on **The Medical Research Community: Driving Progress Together**, p. 9).

The remarkable progress being made against cancers—in particular, improvements in reducing smoking rates and developments in early detection and treatment—is resulting in cancer death rates falling steadily and in a rising number of people who survive a cancer diagnosis. In fact, the age-adjusted overall cancer death rate has declined by 32 percent between 1991 and 2019 in the United States, a reduction that translates into nearly 3.5 million cancer deaths avoided (1). Among children and adolescents with cancer, overall death rates have declined by more than half between 1970 and 2019, largely due to advances in treatment (1). In addition, in the past three years, the number of adults and children living in the United States with a history of cancer rose by more than a million, exceeding an estimated 18 million on January 1, 2022 (2).

The steady decline in the overall cancer death rate can be attributed mainly to the unprecedented progress against lung, colorectal, breast, and prostate cancer, the four most common cancer types in the United States. In fact, during the past three decades, age-adjusted death rates from lung, female breast, and colorectal cancers have decreased by 44, 42, and 53 percent, respectively (3). Furthermore, there have been significant developments against previously intractable cancers, such as melanoma, the deadliest form of skin cancer, fueled by a range of innovative new therapeutics that have moved rapidly from the bench to the clinic and received approval by the U.S. Food and Drug Administration (FDA) (see **Figure 1**, p. 10). Collectively, these advances have led to the increase in five-year relative survival rate for all cancers combined from 49 percent in the mid-1970s to nearly 70 percent from 2011 to 2017, which are the most recent data available (1).

Lung cancer mortality rates have declined from 2015 to 2019

U.S. MEN U.S. WOMEN

Source: (1)

Among the major advances made across the clinical cancer care continuum from August 1, 2021, to July 31, 2022, are the eight new anticancer therapeutics approved for use by FDA (see **Table 4**, p. 69). During this period, FDA also approved two new imaging agents to help visualize cancerous cells, several artificial intelligence-based tools to improve detection and diagnosis of cancers, and new uses for 10 previously approved anticancer therapeutics.

The research that drives progress against cancer is made possible by investments from governments, philanthropic individuals and organizations, and the private sector. In

The Medical Research Community: Driving Progress Together

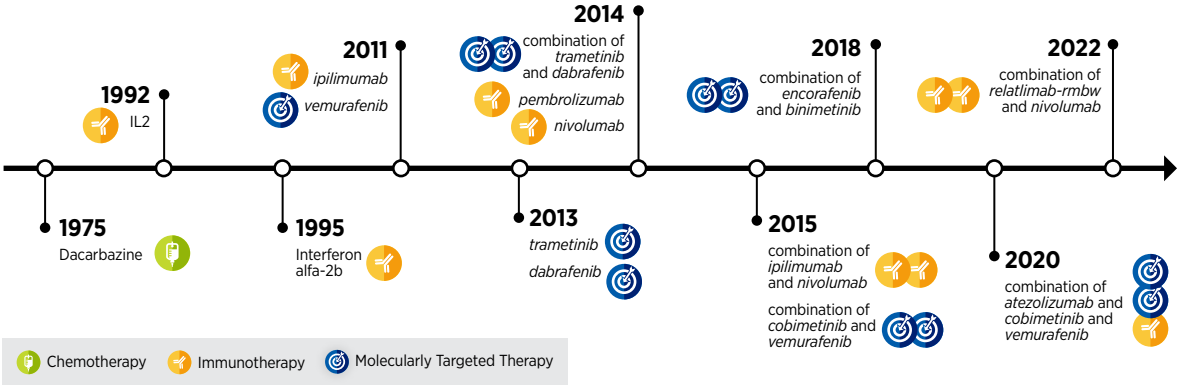
Progress against cancer is made when all stakeholders dedicated to fundamentally changing the burden of cancer work together. Further increasing collaboration will accelerate the pace of future breakthroughs. The key stakeholders are:

Adapted from (1).

the United States, government investments in medical research are administered mostly through the 27 institutes and centers of the National Institutes of Health (NIH). The largest component of NIH is the National Cancer Institute (NCI), which is the federal government's principal agency for cancer research and training. Medical research funded by the public sector contributes significantly to novel drug development, which is critical to saving and improving lives (6,7). Federal investments in government agencies conducting research, such as FDA and the Centers for Disease Control and Prevention (CDC), are also of particular importance.

FIGURE 1

Increasing Treatment Options for Melanoma



Until 2000, the standard of care for patients with metastatic melanoma of the skin was a chemotherapeutic called dacarbazine and/or an immune system stimulant called aldesleukin (Proleukin); however, neither treatment had shown a significant effect on overall survival in clinical trials. From January 1, 2011, to July 31, 2022, the U.S. Food and Drug Administration (FDA) approved five immunotherapeutics for use alone or in combination with either another immunotherapeutic or with molecularly targeted therapeutics in the treatment of patients with metastatic melanoma; these immunotherapeutics are atezolizumab (Tecentriq), ipilimumab (Yervoy), nivolumab (Opdivo), pembrolizumab (Keytruda), and relatlimab-rmbw commonly referred to as relatlimab (Opdualag). In addition, the agency approved six molecularly targeted therapeutics for use alone, or in combination with either another molecularly targeted therapeutic or an immunotherapeutic for treating certain patients with metastatic melanoma; these therapeutics are binimetinib (Mektovi), cobimetinib (Cotellic), dabrafenib (Tafinlar), encorafenib (Braftovi), trametinib (Mekinist), and vemurafenib (Zelboraf). Together, these innovative new therapeutics have helped improve the five-year relative survival rate for individuals diagnosed with metastatic melanoma from 18 percent (2006-2012) to 32 percent (2012-2018), the most recent time for which these data are available) (4,5).

*This timeline focuses on systemic treatments for metastatic melanoma of the skin; other therapeutics have been approved for the prevention of disease recurrence or the treatment of localized lesions. Also not included are therapeutics that are approved for other rarer forms of melanomas. For example, in January 2022, FDA approved tebentafusp (Kimmtrak) for the treatment of certain patients with uveal melanoma, an aggressive cancer of the eye.

Cancer: An Ongoing Public Health Challenge in the United States and Worldwide

Although we have made incredible progress against cancers, this group of devastating diseases continues to be an enormous public health challenge in the United States and around the world. In the United States alone, it is predicted that 1,918,030 new cases of cancer will be diagnosed in 2022 and that 609,360 people will die from the disease (1) (see **Table 1**, p. 11). These estimates do not account for the consequences of COVID-19, which has proven to have an adverse impact across the spectrum of cancer research and patient care including significant declines in cancer screening and diagnosis (8). In addition, data from the past two years have clearly shown the heightened risks of SARS-CoV-2 infection and severe COVID-19 among patients with cancer, albeit COVID-19-related mortality among this population has decreased over time (8,9). Ongoing research will uncover the long-term effects of COVID-19 on cancer outcomes (10).

VARIABLE PROGRESS AMONG STAGES AT DIAGNOSIS AND TYPES OF CANCER

Progress against cancers has not been uniform for all stages of a given type of disease (5). This issue is illustrated by the fact that the five-year relative survival rates for U.S. patients vary widely depending on the stage at diagnosis (5). As one example, among women with breast cancer and people with colorectal cancer, those whose cancer is confined to the breast, or to the colon or rectum, have five-year relative survival rates of 99 percent and 92 percent, respectively, while those whose cancer has spread to a distant site have five-year relative survival rates of 30 percent and 16 percent, respectively (5).

TABLE 1

Estimated* Incidence and Mortality for Selected Cancers

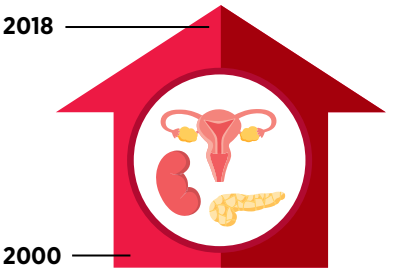
	ESTIMATED 2022 INCIDENCE			ESTIMATED 2022 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	**1,918,030**	**983,160**	**934,870**	**609,360**	**322,090**	**287,270**
Head and Thorax Region						
Brain & other nervous system	25,050	14,170	10,880	18,280	10,710	7,570
Eye & orbit	3,360	1,790	1,570	410	220	190
Tongue	14,490	8,490	6,000	3,020	1,810	1,210
Mouth	14,490	8,490	6,000	3,020	1,810	1,210
Pharynx	19,270	15,670	3,600	3,980	3,140	840
Other oral cavity	2,380	1,660	720	1,440	1,090	350
Larynx	12,470	9,820	2,650	3,820	3,070	750
Lung & bronchus	236,740	117,910	118,830	130,180	68,820	61,360
Breast	290,560	2,710	287,850	43,780	530	43,250
Gastrointestinal (GI) System						
Esophagus	20,640	16,510	4,130	16,410	13,250	3,160
Stomach	26,380	15,900	10,480	11,090	6,690	4,400
Liver & intrahepatic bile duct	41,260	28,600	12,660	30,520	20,420	10,100
Gallbladder & other biliary	12,130	5,710	6,420	4,400	1,830	2,570
Pancreas	62,210	32,970	29,240	49,830	25,970	23,860
Small intestine	11,790	6,290	5,500	1,960	1,110	850
Colon and Rectum	151,030	80,690	70,340	52,580	28,400	24,180
Anus, anal canal, & anorectum	9,440	3,150	6,290	1,670	740	930
Endocrine System						
Thyroid	43,800	11,860	31,940	2,230	1,070	1,160
Urogenital System						
Kidney & renal pelvis	79,000	50,290	28,710	13,920	8,960	4,960
Ovary	19,880	—	19,880	12,810	—	12,810
Penis and other genital organs, male	2,070	2,070	—	470	470	—
Prostate	268,490	268,490	—	34,500	34,500	—
Testis	9,910	9,910	—	460	460	—
Uterine cervix	14,100	—	14,100	4,280	—	4,280
Uterine corpus	65,950	—	65,950	12,550	—	12,550
Urinary bladder	81,180	61,700	19,480	17,100	12,120	4,980
Vulva	6,330	—	6,330	1,560	—	1,560
Vagina and other genital organs, female	8,870	—	8,870	1,630	—	1,630
Skin (excluding basal & squamous)						
Melanoma-skin	99,780	57,180	42,600	7,650	5,080	2,570
Other nonepithelial skin	8,700	5,640	3,060	4,340	2,980	1,360
Hematological System						
Acute lymphocytic leukemia	6,660	3,740	2,920	1,560	880	680
Chronic lymphocytic leukemia	20,160	12,630	7,530	4,410	2,730	1,680
Acute myeloid leukemia	20,050	11,140	8,910	11,540	6,730	4,810
Chronic myeloid leukemia	8,860	5,120	3,740	1,220	670	550
Other leukemia	4,920	3,180	1,740	5,270	3,010	2,260
Hodgkin lymphoma	8,540	4,570	3,970	920	550	370
Non-Hodgkin lymphoma	80,470	44,120	36,350	20,250	11,700	8,550
Myeloma	34,470	19,100	15,370	12,640	7,090	5,550
Other Cancers						
Bones & joints	3,910	2,160	1,750	2,100	1,180	920
Soft tissue (including heart)	13,190	7,590	5,600	5,130	2,740	2,390

*Rounded to the nearest 10.

Source: Estimated new cases are based on 2004-2018 incidence rates reported by the North American Association of Central Cancer Registries (NAACCR). Estimated deaths are based on 2005-2019 U.S. mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention. Table is modified from (1).

- **Overall U.S. cancer incidence** has been **declining** during the **past two decades**, albeit the rates have stabilized more recently.
- However, the **incidence of certain cancers**, such kidney, pancreatic, and uterine cancer, is **rising**.
- For example, **between 2000 and 2018, pancreatic cancer incidence increased** significantly, with the greatest increase observed among **women ages 15 to 34 years**.

Data from (5,11).



An additional challenge that we face is the uneven progress against various cancer types (5). For example, the overall five-year relative survival rates of nearly 91 percent for women with breast cancer and 97 percent for men with prostate cancer stand in stark contrast to the overall five-year relative survival rates of 21 percent for people with liver cancer and less than 12 percent for those with pancreatic cancer (5). While some of these differences could be attributed to early detection of breast and prostate cancers through population level screening (see sidebar on **Ways to Screen for Cancer**, p. 48), disparities in five-year relative survival rates hold true for patients with these four cancer types even when their diseases are diagnosed at an advanced stage. The five-year relative survival rates of greater than 30 percent for advanced-stage female breast and male prostate cancers are significantly higher than the five-year relative survival rates of less than five percent for those with advanced-stage liver or pancreatic cancer (5).

Among children ages one to 14 years, cancer is the second-leading cause of death, and the most diagnosed cancers are leukemia and brain tumors (1). Thanks to extraordinary advances in treatments for childhood leukemia, the age-adjusted mortality rate from the disease has almost halved in the past two decades. Unfortunately, mortality rates from childhood brain and other central nervous system tumors have essentially remained unchanged (5).

Developing new and effective tests for early detection of more types of cancer as well as better treatment options for all cancer types and for all stages of diagnosis could help address the challenges of variable progress against different types of cancer.

DISPARITIES IN PROGRESS FOR CERTAIN POPULATION GROUPS

Cancer health disparities are one of the most pressing public health challenges in the United States. NCI defines cancer health disparities as adverse differences in cancer such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (12) (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?**, p. 13).

As outlined in the *AACR Cancer Disparities Progress Report 2022*, racial and ethnic minorities and other medically underserved U.S. populations shoulder a disproportionately higher burden of cancer (see sidebar on **Disparate Burden of Cancer in the U.S.**, p. 14) (13). As one example, the U.S. Black population has long experienced cancer health disparities. In 1990, the overall cancer death rates for Black people were 33 percent higher than for White people (5). There has been some progress in recent years as evidenced by the narrowing of the gap in cancer death rates between the Black and White populations to 13 percent in 2019, a 60 percent decline in the disparities since 1990 (5,14). However, even in 2019, overall cancer death rates were higher among Black men and women compared to all other U.S. racial and ethnic groups (14).

Sexual and gender minorities (SGM) are another U.S. population that experiences cancer health disparities. According to a new report, gay men are more likely than heterosexual men to report lifetime diagnoses of cancers, and gay men and lesbian women are more frequently unable to afford many types of health care services compared to heterosexual men and women (15). Unfortunately, there are limited data on the epidemiology of cancer incidence and outcomes among SGM individuals making it difficult to evaluate the true burden of cancer in this underserved population. It is imperative that researchers collect disaggregated data by sexual orientation and gender identity, as well as within sexual minority groups (e.g., gay versus bisexual) and gender minority groups (e.g., transgender versus nonbinary) to accurately capture cancer epidemiology in these heterogeneous populations (13).

Research has identified complex and interrelated factors, often referred to as the social determinants of health, including socioeconomic, cultural, behavioral, environmental, and clinical factors that contribute to cancer health disparities. It is increasingly evident that structural racism and systemic injustices cause adverse differences in social determinants of health, creating conditions that perpetuate health inequities, including cancer health disparities (see sidebar on **Why Do U.S. Cancer Health Disparities Exist?**, p. 15).

One of the drivers of cancer health disparities is general health of a population group. For instance, individuals with underlying health conditions, such as diabetes, or those infected with certain pathogens, such as human immunodeficiency virus (HIV), experience a greater burden of cancer (see sidebar on **Cancer Burden Among People Living with HIV**, p. 16). It should be noted that individuals with intersectional identities often experience multilevel barriers to optimal health care

Which U.S. Population Groups Experience Cancer Health Disparities?

According to the National Cancer Institute (NCI), cancer health disparities are adverse differences in cancer such as the number of new cases and deaths, cancer-related health complications, quality of life after cancer treatment, financial burden, screening rates, and stage at diagnosis that are shouldered by certain population groups including (12):

Individuals belonging to certain ancestry, racial or ethnic minority

Individuals of low socioeconomic status

Individuals who lack or have limited health insurance coverage

Residents in certain geographic locations, including rural areas

Individuals belonging to sexual and gender minorities

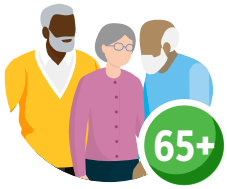
Immigrants

Refugees or asylum seekers

Individuals with disabilities

Adolescents and young adults (AYA)

Older adults



Adapted from (13).

SOCIAL DETERMINANTS OF HEALTH

Disparate Burden of Cancer in the U.S.

Certain population groups in the U.S. (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?**, p. 13) shoulder a disproportionate burden of cancer. Recent examples of disparate cancer incidence and outcomes are provided here. Disparities in other aspects of cancer care are highlighted in relevant sections throughout the report. A more in-depth discussion of cancer health disparities and gaps in our knowledge in addressing these inequalities, as well as a Call to Action, is included in *AACR Cancer Disparities Progress Report 2022* (13).

TWICE as high	The **incidence of gastric cancer** is nearly twice as high in **American Indian/Alaska Native, Asian, Black, and Hispanic individuals** compared to non-Hispanic White individuals (5).
MORE likely	**Native Hawaiian or Other Pacific Islander patients** are 38 percent **more likely to present with advanced-stage head and neck cancer** and 18 percent **more likely to die** from the disease compared to non-Hispanic White patients (16).
34% higher	**Lung cancer death rates** are 34 percent higher **among rural county residents** compared to those living in urban counties (17).
MORE likely	**Gay men** (12 percent) are more likely than heterosexual men (8 percent) to **report lifetime diagnoses of cancer** (15).
TWICE the risk	**Adolescent and young adult cancer survivors** have nearly twice the **risk of dying from a new cancer** compared to the general population (18).
HIGHER odds	**Patients living in areas with the lowest levels of education and income** have 12 percent and 13 percent higher odds, respectively, of being **diagnosed with advanced-stage lung cancer** (19).

that adversely impact cancer incidence and outcomes. As one example, among individuals living with HIV, those who are from racial and ethnical minority populations may experience worse cancer health disparities (20). Understanding the biological drivers of cancer health disparities in marginalized populations with an underlying HIV/AIDS diagnosis is an area of active investigation (20).

Considering that a significant proportion of the U.S. population is affected by cancer health disparities, it is important that public health experts intensify research efforts designed to improve our understanding and mitigating of these disparities. Only with new insights obtained through innovative research, including basic science using biospecimens from diverse populations, clinical trials involving participants from all sociodemographic backgrounds, and health care delivery research, will we develop and implement interventions that may eventually eliminate cancers for all populations.

THE GROWING BURDEN OF CANCER

The public health challenge posed by cancer is predicted to grow considerably in the coming decades unless we develop and implement more effective strategies for cancer prevention, early detection, and treatment (26). In the United States alone, the number of new cancer cases diagnosed each year is expected to reach nearly 2.3 million by 2040 (26). This is largely because cancer is primarily a disease of aging; 80 percent of U.S. cancer diagnoses occur among those who are 55 or older; 57 percent of diagnoses occur among those 65 and older (1), and this segment of the U.S. population is expected to grow from 54.1 million in 2019 to nearly 81 million in 2040 (27). Also contributing to the projected increase in the number of U.S. cancer cases are high rates of obesity and physical inactivity, which are both linked to some common types of cancer, and the continued use of tobacco products among certain U.S. populations.

Why Do U.S. Cancer Health Disparities Exist?

Complex and interrelated factors contribute to cancer health disparities in the United States. For racial and ethnic minorities, adverse differences in many, if not all, of these factors are directly influenced by structural and systemic racism (e.g., discrimination, segregation). The factors contributing to differences or inequalities include:

SOCIOECONOMIC FACTORS

- Education
- Income
- Employment
- Health literacy and numeracy
- English language proficiency

CLINICAL FACTORS

- Access to quality health care that is culturally appropriate
- Access to health insurance
- Cultural fluency of health care provider

BEHAVIORAL AND PSYCHOLOGICAL FACTORS

- Tobacco use
- Alcohol use
- Stress
- Access to safe spaces for physical activity
- Access to healthy nutritional choices
- Access and adherence to risk reduction/preventive care
- Access to culturally tailored mental health care

CULTURAL FACTORS

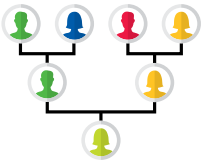
- Beliefs
- Health-related beliefs

ENVIRONMENTAL FACTORS

- Transportation
- Housing
- Geographic location

GENETIC AND BIOLOGICAL FACTORS

- Ancestry-related genetic differences



GENERAL HEALTH

- Having other health conditions or comorbidities, e.g., infection with human immunodeficiency virus (HIV); having diabetes.

Adapted from (21).

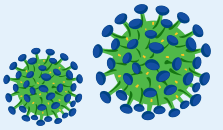
Progress has been made toward reducing cancer incidence in the United States; new cancer cases have declined 10 percent from their peak in 1992 to 2019, the year for which the most recent data are reported (5). However, overall cancer incidence has been rising among the U.S. adolescent and young adult (AYA) population (ages 15 to 39), which has seen nearly a 20 percent increase in cancer incidence from 2000 to 2019 (5). In addition, the incidence of certain cancer types is steadily increasing, specifically among people younger than 50. As one example, many recent studies have reported an increase in the incidence of early-onset colorectal cancer among those age 49 and younger (28,29). The reasons behind rising cases of early-onset colorectal cancers are not completely understood but is presumed to be multifactorial, including contributions of modifiable lifestyle factors such as unhealthy diet and physical inactivity as well as factors that alter the gut microbiome such as use of antibiotics. To reduce the burden of early-onset colorectal cancer, many professional societies have modified their screening guidelines to recommend starting colorectal cancer screening at an earlier age. Additionally, researchers are evaluating new and improved strategies including genetic

AGE-ADJUSTED INCIDENCE RATE OF COLORECTAL CANCER (PER 100,000)

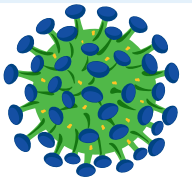
Source: (5)

Cancer Burden Among People Living with HIV

Individuals living with human immunodeficiency virus (HIV) have a higher risk of developing certain cancers. The higher risk is attributed to HIV infection, which weakens the immune system, as well as the greater prevalence of certain risk factors (e.g., smoking) among this population.



- HIV-infected individuals have a significantly elevated risk of Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer. These are referred to as AIDS-defining cancers because they are linked to and/or worsened by HIV-associated immunosuppression.
- HIV-infected individuals also have an elevated risk for certain other cancers, such as anal, liver, and lung cancer. These are considered non-AIDS-defining cancers.



Since the introduction of highly active antiretroviral therapy (HAART) for treatment of HIV in 1996, the epidemiology of HIV-associated cancers has evolved substantially.

- For example, prior to HAART (1991-1995), HIV-infected people had a 2,800-fold higher risk for KS compared to the general population. Since HAART (2000-2010) there has been steady decline in incidence of KS; however, rates remain 800-fold higher than in the general population.

- Decline in mortality among HIV-infected individuals since the introduction of HAART has resulted in the growth and aging of this population. In 1996, 2.5 percent of people with AIDS in the U.S. were ≥ 60 years old compared to 15.4 percent in 2013.

Because cancer risk increases with age, the burden of cancer in HIV-infected people has also increased.

- While the incidence of AIDS-defining cancers is declining because of better management of disease through HAART, incidence of non-AIDS-defining cancers, those with high prevalence among people with HIV (e.g., anal or lung cancer) as well as those that are common in the general population (e.g., breast or prostate cancer), is increasing.
- An estimated 134,986 years of life were lost to cancers during 2006-2015 among individuals living with HIV.

As the population living with HIV continues to grow and age, the burden of cancers, particularly non-AIDS-defining cancers, will continue to rise. **It is estimated that in 2030, the most common cancers among HIV-infected population will be prostate, lung, and liver cancer.** It is imperative that public health experts focus on improving cancer prevention, early detection, and treatment for this population.

Data from (22-25).

testing and others for prevention and early detection of colorectal cancer in the younger population (28).

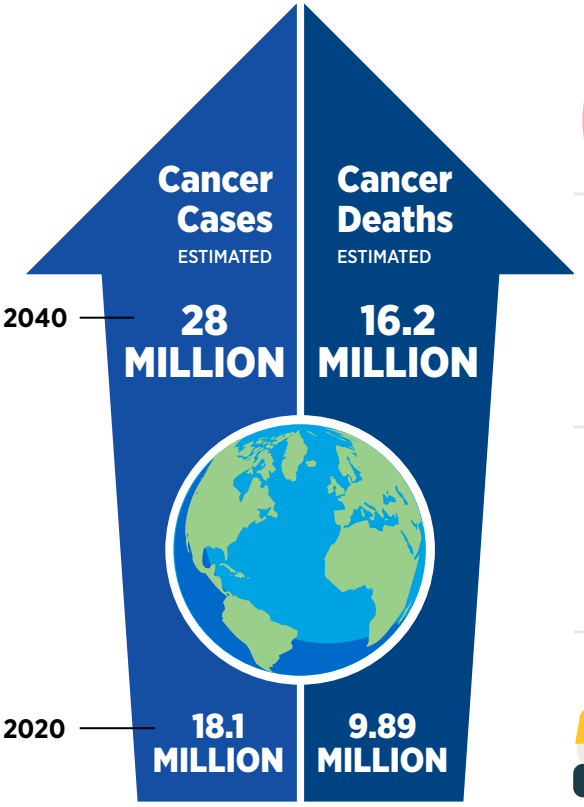
THE GLOBAL CHALLENGE OF CANCER

Beyond the United States, cancer is an ongoing global challenge (see sidebar on **Global Burden of Cancer**, p. 17). According to a new analysis, there were an estimated 17.2 million new cancer cases (excluding nonmelanoma skin cancer) and 10 million cancer deaths globally, in 2019 (30). The study evaluated cancer burden from 204 countries and territories as indicated by cancer-related deaths, as well as disability-adjusted life years (DALYs) and years of life lost (YLLs), which are two measures of cancer morbidity. Researchers found that among the 22 groups of diseases and injuries analyzed, cancer was second only to cardiovascular disease in the number of deaths, DALYs, and YLLs (30). The five leading causes of cancer-related morbidity among men and women combined were lung cancer, colorectal cancer, stomach cancer, breast cancer, and liver cancer.

The study also indicated that, although there were increases in the absolute numbers of both global cancer deaths and

Global Burden of Cancer

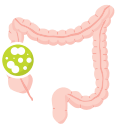
Cancer poses a major challenge to public health across the globe, as reflected by the rising number of new cancer diagnoses and cancer deaths around the world. The disparate burden of cancer based on the sociodemographic index (SDI) of a country (a composite measure of social and economic development that accounts for income per capita, average years of education, and total fertility rate for people younger than 25) highlights key barriers to achieving global health equity. The following examples offer a broad view of the global burden of cancer.



Data from https://gco.iarc.fr/.

Tracheal, bronchus, and lung cancers are the leading causes of cancer deaths worldwide. There were 2.04 million deaths from tracheal, bronchus, and lung cancers in 2019 (34). Smoking contributed to more than 64 percent of these deaths.

Breast cancer was the leading cause of cancer-related deaths among women in 2019 (30). There are stark disparities based on the socioeconomic status of a country, prompting researchers worldwide to provide strategies to influence global policy and improve lives of patients irrespective of where they live (35).



Diagnoses and deaths from colorectal cancer more than doubled over the past three decades (36). A substantial rise in new cases has been observed in adults younger than 50, particularly in countries with a high SDI. Poor diet, smoking, and alcohol were the main risk factors.

There were 1.19 million cancer cases and 396,000 cancer deaths among adolescents and young adults (people ages 15 to 39) in 2019 (37). The highest incidence was observed in countries with higher SDI while the highest deaths occurred in countries with a lower SDI.

new cases from 2010 to 2019, the age-standardized mortality and incidence rates decreased by six percent and one percent, respectively (30). These trends, however, precede the setbacks in cancer care and outcomes that have been caused by the COVID-19 pandemic. Global health experts are also concerned about the consequences of the ongoing wars that have displaced populations, further destroying health care systems, disrupting social services, and increasing risk of infectious disease transmission (31). Considering the devastating impact of these global crises on the entire continuum of cancer research and patient care as well as the growth of the global population age 65 and older (32), researchers caution that the burden of cancer worldwide may rise significantly in the coming decades.

Another concern among global public health experts is that, while age-standardized mortality and incidence rates are declining overall, the reduction in rates appears to be driven by countries with a higher sociodemographic index (SDI)—a composite measure of the social and economic development of a country that considers income per capita, average years of education, and total fertility rate for people younger than 25. The data indicate that age-standardized cancer incidence and mortality rates are increasing in countries with lower SDI (33).

To ensure that progress against cancer is equitable worldwide, it is imperative that the global medical research community work together and share best practices to implement newer and more effective strategies that incorporate local needs and knowledge into tailored national cancer control plans. Public health experts have identified several priorities based on present and future needs of low resource countries, including reducing the burden of advanced cancers; improving access, affordability, and outcomes of treatment, utilizing value-based care; fostering implementation research; and leveraging technology to improve cancer control (33).

Funding Cancer Research: A Vital Investment

Cancer exerts an immense toll because of the number of lives it affects each year and through its significant economic impact. The direct medical costs of cancer care are one measure of the financial impact of cancer, and in the United States alone, they were estimated to be $183 billion in 2015, the last year for which these data are currently available; this cost is projected to increase to $246 billion by 2030 (1). These numbers do not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, which are also extremely high. Notably, cancer patients in the United States shouldered an economic burden of $21 billion in 2019 from out-of-pocket costs and other related expenses, which is nearly 3.5 times the amount of approximately $6 billion in NCI funding for cancer research in the same year (38).

With the number of cancer cases projected to increase in the coming decades, we can be certain that both the direct and indirect costs will also escalate. The rising personal and economic burden of cancer underscores the urgent need for more research so that we can accelerate the pace of progress against cancer.

Recent advances in cancer prevention, detection, and treatment, many of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers from across the spectrum of cancer science and medicine. Much of their work, as well as that of FDA—the federal regulatory agency that assures the safety and efficacy of medical devices and therapeutic advances—is supported by funds from the federal government. The consecutive increases for the NIH budget in the last seven fiscal years have helped maintain the momentum of progress (see **Investments in Research Fuel a Healthier Future**, p. 127). To keep up with the pace of scientific and technological innovation, it is imperative, however, that Congress continue to provide sustained, robust, and predictable increases in investments in the federal agencies that are vital for fueling progress against cancer, in particular, NIH, NCI, FDA, and CDC, in the years ahead (see **AACR Call to Action**, p. 140).

The **estimated cost of care** for the **15 most prevalent cancers in the U.S.** in 2018, among privately insured patients <65, was **$156.2 billion** (39).

Understanding How Cancer Develops

IN THIS SECTION YOU WILL LEARN:

- Research provides our understanding of the biology of cancer, which is not one disease, but a collection of diseases characterized by the uncontrolled growth of cells.
- Genetic mutations underpin cancer initiation and development in most cases; mutations are inherited in about 10 percent of patients.
- Cancer initiation and progression are strongly influenced by interactions of cancer cells with cellular and molecular factors in their environment, referred to as the tumor microenvironment.
- Identification of genetic, epigenetic, protein, and cellular alterations that drive cancer are an important part of the cancer care decision-making process and form the foundation of precision medicine.

The term cancer describes a collection of diseases characterized by the inability of a cell to respond to normal biological cues that regulate processes including cell division, growth, and life span. When cells acquire these traits, they begin to divide uncontrollably and accumulate in organs and tissues forming a mass called a tumor, whereas in the blood or bone marrow they crowd out normal cells. Cancer cells use the blood and lymphatic systems to leave the organ of origin and move to distant sites. Growth of cancer cells in another organ distant from its original site is called metastasis and is the primary cause of death in most cancers. Understanding the biological mechanisms underlying tumor initiation and metastasis and identifying ways to prevent these processes are key focus areas of ongoing research (40,41). Our understanding of the hallmarks that define cancer development has increased tremendously in the past two decades, thanks to major advances in basic research resulting from generous federal investments (42) (see sidebar on **What Is Basic Research and How Does It Drive Progress Against Cancer?**, p. 20).

Cancer Development: Influences Inside the Cell

Cells of the human body rely on instructions in their genetic material, known as deoxyribonucleic acid (DNA), to function. DNA is a complex molecule made up of four types of building blocks, called bases, each of which are unique molecules, designated A, T, C, and G (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 21). Anywhere from 50 to 250 million of these bases are linked together to form individual DNA strands. Two strands of the same length are then paired together to form a helical structure, which is packaged with proteins, known as histones, into structures called chromosomes that are located inside the nucleus of a cell.

Each chromosome contains hundreds to thousands of genes, which are segments of DNA that contain the code for a protein, the functional unit of the cell. To make a protein, a cell copies the "message" embedded in a gene from DNA to make another type of molecule called ribonucleic acid (RNA) in a process called transcription. The cell can make many copies of this messenger RNA (mRNA) from a single sequence of DNA, amplifying the amount of the message in the cell. The cell then "translates" the information from mRNA into proteins. It is important to note that cellular functions are controlled by many additional layers of complexity. For example, not all parts of DNA make mRNA and not all RNA molecules make proteins, but both DNA and RNA have important roles in determining overall cell function (44,45).

Cancers arise when there are alterations in the DNA sequence, referred to as mutations (see sidebar on **Alterations That Lead to Cancer**, p. 23). The mutations change the way the cell reads DNA, which can alter the sequence or amount of mRNA and the resulting protein that is produced. Mutations can develop differently for each individual and are attributed to a range of genetic as well as environmental factors. Therefore, a patient's cancer can have one or more unique combinations of genetic mutations. Furthermore, as cancer cells divide, new mutations can arise. Several research efforts are aimed at building databases that catalogue different types of mutations contributing to cancer initiation and progression (46). The following section describes the types of mutations that occur in the DNA and how these changes alter the normal functions of the cell, which leads to cancer.

DNA MUTATIONS

Most cancer-causing mutations are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of environmental exposures, lifestyle

What Is Basic Research and How Does It Drive Progress Against Cancer?

The National Institutes of Health (NIH) defines basic research as "the systematic study directed toward fuller knowledge or understanding of the fundamental aspects of a phenomenon and of observable facts without specific applications toward processes or products in mind." Basic research has broad implications because it is fundamental to our understanding and treatment of human diseases, including cancer. NIH spends more than half of its budget supporting basic research (43). NIH-supported basic research projects significantly contribute to novel target identification and drug development (7).

Selected examples of basic research discoveries that have transformed the landscape of cancer treatment are:

LAG-3, a protein expressed by some immune cells, is used as a receptor for certain proteins on cancer cells to evade detection and elimination by the immune system. Identification of the *LAG-3* gene in 1990 led to the FDA approval of the first immune checkpoint inhibitor against LAG-3, relatlimab (Opdualag) (first approval in eight years against a novel immune checkpoint target) in 2022, **to treat certain patients with melanoma** (see **Progress Across the Spectrum of Cancer Treatment**, p. 67).

Basic research led to the discovery in 1960s of a unique fusion of chromosomes 9 and 22, termed the Philadelphia chromosome, specifically in cells of patients with chronic myelogenous leukemia (CML). This has led to several drugs that target this gene fusion including the recent FDA approval of asciminib (Scemblix) **to treat patients who are resistant to current therapies** (see **Expanding Treatment Options for Patients with Blood Cancers**, p. 78).

Discovery of the gene *VHL* and its function in regulating HIF-2α led to the recent FDA approval of the first direct inhibitor of HIF-2α, belzutifan (Welireg), for the **treatment of renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors** in adults with von Hippel Lindau disease (see **Adding Precision to the Treatment of Rare Cancers**, p. 74).

factors, or health conditions that fuel chronic inflammation. These acquired mutations are referred to as somatic mutations.

In about 10 percent of cancer cases the mutations are inherited (see **Table 2**, p. 22). When multiple individuals in a family carry a mutation in a gene that is associated with cancer-causing processes, and there is strong evidence that the mutation significantly increases risk of cancer, these types of inherited mutations are called "pathogenic." Decades of research have led to the identification of numerous genes that are associated with cancers as well as specific inherited mutations in those genes that are pathogenic (see **Table 2**, p. 22) (47).

Pathogenic mutations continue to be identified by genetically profiling cells from different types of cancer and decoding these cancer-causing mutations. For example, a recent study of 214,000 patients identified seven new pathogenic mutations that were associated with increased risk of developing leukemia, or stomach, pancreatic, kidney, and bladder cancers, and intrahepatic bile duct tumors, expanding our understanding of what types of pathogenic mutations lead to cancer (48).

One example of inherited mutations is those in *BRCA1/2* genes, which are important for repairing damaged DNA in cells. Mutations in either *BRCA1* or *BRCA2* can increase the risk of breast, ovarian, pancreatic, and prostate cancer. New data demonstrate that mutations in *BRCA1/2* genes can also increase the risk of biliary tract cancer, esophageal, and/or gastric cancer, expanding our understanding of the role of pathogenic mutations (49).

These discoveries demonstrate the far-reaching contributions of cancer research that help expand our understanding of how cancer develops.

RNA ALTERATIONS

As described earlier, when a cell "reads" a gene, it copies the information from the DNA into an RNA molecule called messenger RNA or mRNA. By changing the number of times DNA is copied into mRNA, the cell can increase or decrease

Genetic and Epigenetic Control of Cell Function

The genetic material of a cell comprises strings of **deoxyribonucleic acid (DNA)**, a complex molecule comprised of four units called bases, which are designated A, C, G, and T.

DNA bases are organized into **genes**. The order, or sequence, of the bases provides the code used by the cell to produce **ribonucleic acid (RNA)**, which subsequently is used by cells to generate the various proteins that cells need to function.

The entirety of a person's DNA is called the **genome**. Almost every cell in the body contains at least one copy of the genome. The genome is packaged together with proteins known as histones into structures called **chromosomes** within a nucleus of the cell.

Special factors, called **epigenetic marks**, can tag DNA or attach to histones. The presence or absence of these factors determines whether a gene is accessible for reading. The sum of these marks across the entire genome is called the **epigenome**.

The accessible genes within each cell are read by specialized molecular machinery to produce the proteins that ultimately define the function of the cell and the tissue in which the cell resides.

Adapted from (13).

the amount of the mRNA, which helps control the amount of protein a cell makes; the cellular levels of a protein can drastically affect cell function. Furthermore, a cell is usually making copies of mRNA from hundreds to thousands of different genes at once, producing many different types of proteins, each of which performs different functions and influences the cell's biology. Advances in nucleic acid sequencing technology have allowed researchers to determine the sequences of genes, as well as the types and levels of mRNA produced, to create molecular profiles that often match the function of the cell. Profiling cancer cells from a tumor and comparing the profile to that of cells from the normal tissue helps researchers identify specific characteristics that contribute to cancer development.

Examining mRNA in cancer cells has some advantages over exclusively studying DNA. A key reason for this is that mRNA is what makes protein, and therefore changes that occur in mRNA are more consequential. Researchers in one study looked at the ability of mRNA sequencing to detect the presence of a type of mutation called a gene fusion, which occurs in certain cancers (see sidebar on **Alterations That Lead to Cancer**, p. 23). The researchers were not only able to identify the same gene fusions detected by DNA testing using mRNA sequencing, but also to identify additional fusions that were not originally picked up during DNA analysis. Furthermore, by analyzing the mRNA sequence, researchers were able to identify which genes were fused, and for a subset of patients, this led to the use of targeted treatments against the mutation which was previously unknown (51).

Normal cells copy the message from DNA in pieces of mRNA that are assembled in a process called splicing to complete the message. In cancer cells, this process can be altered to generate abnormal proteins, which can fuel uncontrolled cell proliferation and growth (see sidebar on **Alterations That Lead to Cancer**, p. 23). For instance, in non-small cell lung cancer, the gene *MET* can become alternately spliced, generating an abnormal protein called METex14. If genetic tests reveal the presence of this alternately spliced mRNA, MET-targeted therapeutics can be used for the treatment of such patients (52,53).

PROTEIN MODIFICATIONS

Cells use networks of proteins, often referred to as signaling networks, to sense important information regarding internal conditions such as cellular energy levels as well as external conditions like temperature, integrating this information to mount a cellular response; for example, a cell can increase the level of energy production to grow and divide based on sensing external stimuli permitting it to do so; conversely, an

TABLE 2

Inherited Cancer Risk

Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
Basal cell carcinoma and medulloblastoma	Basal cell nevus syndrome	*PTCH1, PTCH2, SUFU*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid, and endometrial cancers	Cowden syndrome	*PTEN*
Breast and stomach cancers	Diffuse gastric and lobular breast cancer syndrome	*CDH1*
Colorectal, duodenal, stomach, and thyroid cancers	MYH associated polyposis	*MUTYH*
Colorectal cancer, medulloblastoma	Familial adenomatous polyposis	*APC*
Melanoma and pancreatic cancer	Familial atypical multiple mole–melanoma syndrome	*CDKN2A*
Glioblastoma and melanoma	Familial glioma-melanoma syndrome	*CDKN2A*
Retinal cancer, pineoblastoma, and bone and soft tissue sarcomas	Retinoblastoma predisposition syndrome	*RB1*
Leukemia and myelodysplastic syndrome (MDS)	Inherited bone marrow failure syndromes, such as Fanconi anemia and telomere syndromes	*FANCC, FANC, FANCB, FANCS, BRCA1, BRCA1, TERT, TERC*
Kidney cancer and uterine fibroids	Hereditary leiomyomatosis and renal cell cancer	*FH*
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	*PRSS1, SPINK1*
Leukemias, breast cancer, glioblastoma, choroid plexus carcinoma, adrenocortical carcinoma, and bone and soft tissue cancers	Li-Fraumeni syndrome	*TP53*
Low grade gliomas, neurofibromas, neurofibrosarcomas, meningiomas, and ependymomas	Neurofibromatosis type I and neurofibromatosis type II	*NF1 and NF2*
Glioblastoma, colorectal cancer, and endometrial cancer	Brain tumor polyposis type I	*MLH1, PMS2*
Medulloblastoma, abdominal desmoid tumors, and colorectal cancer	Brain tumor polyposis type II	*APC*
Colorectal and endometrial cancers	Lynch syndrome	*EPCAM, MLH1, MSH2, MSH6, PMS2*
Rhabdoid tumors of brain, kidney and extra-renal sites	Rhabdoid predisposition syndrome	*hSNFS, INI1*
Subependymal giant cell astrocytoma, renal angiolipomas, and cardiac rhabdomyomas	Tuberous sclerosis complex	*TSC1 and TSC2*
Leukemias, lymphomas, and MDS	Hereditary myeloid malignancy syndromes, such as familial MDS/Acute myeloid leukemias	*RUNX1, GATA2, CEBPA, ETV6, DDX41, ANKRD26, ATG2B/GSKIP*
Pineoblastoma, pleuro-pulmonary blastoma, lymphoma and glioblastoma	DICER syndrome	*DICER1*
Pancreatic cancer, pituitary adenomas, benign skin and fat tumors	Multiple endocrine neoplasia 1	*MEN1*
Thyroid cancer and pheochromocytoma	Multiple endocrine neoplasia 2	*RET, NTRK1*
Pancreatic, liver, lung, breast, ovarian, uterine, and testicular cancers	Peutz–Jeghers syndrome	*STK11/LKB1*
Tumors of the spinal cord, cerebellum, retina, adrenals, and kidneys	von Hippel-Lindau syndrome	*VHL*
Kidney cancer	Wilms' tumor	*WT1*
Skin cancer	Xeroderma pigmentosum	*XPD, XPB, XPA*

This list is not meant to be exhaustive, but contains some of the more commonly occurring cancer syndromes.

Source: http://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq and https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers

Adapted from (21).

Alterations That Lead to Cancer

Alterations including the types of genetic mutation known to lead to cancer include:

SINGLE BASE CHANGES

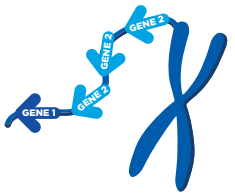
Deletion, insertion, or substitution of a single base (designated A, T, G, C) can result in new proteins, altered versions of normal proteins, loss of protein function, or changed amount of the protein produced, which can lead to cancer.

GENE FUSION

This occurs when two separate genes become joined together leading to the production of a new protein or different amount of protein. Gene fusions can occur when two different chromosomes break, and the pieces connect or fuse with each other.

EXTRA COPIES OF GENES (GENE AMPLIFICATION)

Higher quantities of certain proteins can result in enhanced cell survival and growth, leading to cancer.

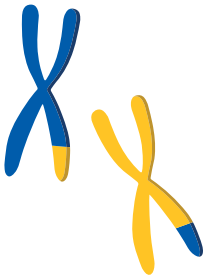


DELETIONS

Loss of DNA can result in loss of genes necessary to regulate the processes that control normal cell growth, division, and life span, leading to cancer development.

STRUCTURAL VARIATIONS

Exchange of DNA between chromosomes can alter multiple genes at once. It can sometimes lead to the fusion of two separate genes, generating entirely new proteins that can drive the development of cancer.

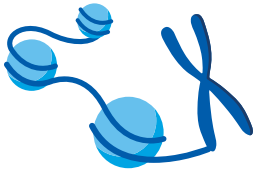


CANCER-RELATED ALTERNATIVE SPLICING

Normal cells copy the message from DNA in pieces of RNA that are assembled in a process called splicing to complete the message. In cancer cells, this process can be altered to generate abnormal proteins, that fuel uncontrolled cell proliferation and growth.

MUTATIONS THAT ALTER THE EPIGENOME

Several proteins read, write, or erase epigenetic marks on DNA or the histones around which DNA is packaged. Mutations in these reader and writer proteins can lead to cancer by altering the activation or silencing of genes needed to control cell growth and division processes.



Of note, cells acquire mutations over time, but not all mutations cause cancer. In addition, not all mutations found in a cancer cell drive cancer development.

Adapted from (50).

unhealthy cell, upon sensing factors released by the immune system, can initiate a programmed sequence of events that leads to its elimination before it can become cancerous. Importantly, cancer cells can often alter the signaling networks, through mutations, upregulation, or modification of proteins, to suit their development and progression. By doing this, they no longer respond to normal cues, leading to uncontrolled cell division or evasion of cell death.

Analyses of DNA or mRNA cannot always reliably predict changes in the level or function of the corresponding proteins and how those may affect signaling networks. Proteomics—the comprehensive analysis of all the proteins inside a cell—is extremely important in cancer research and has proven to be a powerful tool to gain novel insights into a patient's tumor that cannot be realized by genomics alone.

Researchers strongly believe that when used together, cancer proteomics and genomics can truly open new opportunities in the diagnosis, prognosis, and treatment of cancers and transform the landscape of patient care. According to NCI, proteogenomics is defined as the study of how information about the DNA in a cell or organism relates to the proteins made by that cell or organism.

Although this is an emerging area of investigation, several major NCI programs including Clinical Proteomics Tumor Analysis Consortium (CPTAC) are studying how proteins and the signaling networks associated with them are different between cancers. Furthermore, several research groups are utilizing information about signaling changes to identify how different cancer types will respond to different types of cancer therapy combinations (54,55).

EPIGENETIC CHANGES

In addition to genetic mutations, changes caused by chemical modifications of DNA and/or the proteins associated with it, termed epigenetic modifications, can lead to cancer development (see sidebar on **Alterations That Lead to Cancer**, p. 23). Epigenetic modifications regulate how and when our genes are turned on or off. Specialized proteins add or erase unique epigenetic modifications to and from DNA and histones (56). In contrast to genetic mutations, epigenetic changes are often reversible, providing an opportunity for therapeutic intervention.

Our understanding of the epigenetic contributions to cancer development is constantly evolving. As one example, one recent study found that when mutations occur in areas of the DNA that do not code for a gene, this leads to epigenetic modifications many bases away from the gene (57). This means that even when a mutation does not occur within a gene, it can still have far-reaching consequences for the development of cancer through epigenetic effects.

Emerging evidence shows that environmental influences such as diet, stress, smoking tobacco products, and exposure to pollutants can result in epigenetic changes. Understanding these influences is especially important for groups who continue to be disproportionately and negatively affected by environmental influences, such as racial and ethnic minorities and other underserved populations, as discussed in detail in the recently released *AACR Cancer Disparities Progress Report 2022* (13).

Advanced age has been shown to induce epigenetic changes. To understand this phenomenon, researchers have developed 'epigenetic clocks' that estimate an individual's epigenetic age based on modifications present on a person's DNA. Previous studies have indicated how advanced epigenetic age can increase the risk of cancer development (58).

Accelerated epigenetic aging has also been shown in patients treated with certain types of cancer therapies regardless of their biological age, which may explain why cancer survivors can develop side effects, such as "excess heart age." In one study that looked at epigenetic changes in whole blood cells in early-stage breast cancer patients undergoing surgery and radiotherapy, it was found that there was significant epigenetic age acceleration, which affected certain immune cells (59).

TUMOR HETEROGENEITY

The changes in DNA, RNA, and protein can vary among subsets of cells within a single tumor. The phenomenon used to describe cells with different mutations in a single tumor is called tumor heterogeneity. Tumor heterogeneity fuels the cancer's ability to grow faster and metastasize, resist therapy, and evade destruction by the immune system. Fortunately, the adoption of cutting-edge technologies such as genetic sequencing and single cell profiling has allowed researchers to identify the different mutations within subsets of cells in a tumor with a high resolution (60). Additionally, current research is using predictive mathematical models to understand how different groups of cells within a tumor become resistant to therapy and how these unique groups may respond to different types of therapies so they can be treated more effectively (61).

Cancer Development: Influences Outside the Cell

Cancer arises due to the disruption of normal cellular functions through genetic and epigenetic changes in a cell. Once cancer is initiated, however, complex interactions between cancer cells and their surrounding environment—known as the tumor microenvironment—contribute to disease progression (see sidebar on **Cancer Growth: Local and Systemic Influences**, p. 25). For instance, cancer cells can release molecules that shape their surrounding environment to provide them with nutrients, oxygen, and a supportive structure. This reorganization also aids in the process of metastasis of cancer cells through blood and lymphatic systems.

THE BLOOD SYSTEM

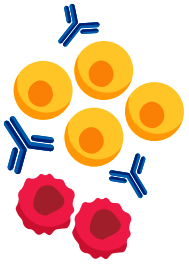
Because cancer cells grow and divide rapidly, they require high levels of oxygen and nutrients to fuel their growth. To keep up with this demand, tumors release factors into the surrounding environment that increase the amount of blood vessels, a process called angiogenesis. Blood vessels carry nutrients and oxygen to the tumor cells while simultaneously removing waste and carbon dioxide. By increasing blood vessel formation around tumors, cancer cells increase access to these components. Therapeutics that block angiogenesis, therefore, can limit access to these factors, restricting a tumor's ability to grow, divide, and metastasize.

Advances in cancer therapeutics over the past two decades have led to the development of inhibitors of angiogenesis, such as those that target the protein VEGF, which is a central regulator of angiogenesis; targeting of this protein inhibits the tumor blood supply. The first anti-angiogenic therapy to be approved by FDA, bevacizumab (Avastin) in 2004 was followed by several other drugs including the most recent approval of tivozanib (Fotivda) in 2021.

Cancer Growth: Local and Systemic Influences

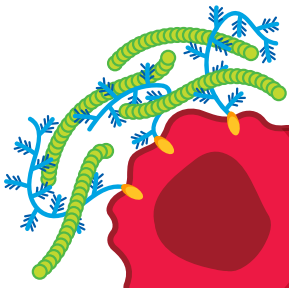
Solid tumors are much more complex than an isolated mass of proliferating cancer cells. Cancer development is strongly influenced by interactions between cancer cells with numerous factors in their environment. Among the components of the tumor microenvironment are the following:

Immune cells can identify and eliminate cancer cells, although in many cases the immune system is suppressed, permitting the formation and progression of a tumor. However, in some situations of chronic inflammation, the immune system can promote cancer development and progression.

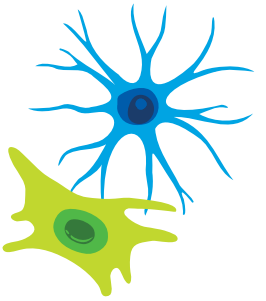


Cancer cells can stimulate a process called tumor angiogenesis, the growth of **blood and lymphatic vessel networks**, which supply the cancer cells with the nutrients and oxygen required for rapid growth and survival and provide a route for cancer cell escape to distant sites (metastasis).

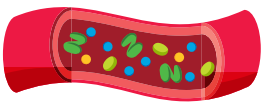
The **matrix** surrounds the tumor and provides structural and biochemical support. This ultimately regulates proliferation of cancer cells, supports tumor growth, and eventually aids in tumor metastasis.



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



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



Adapted from (21).

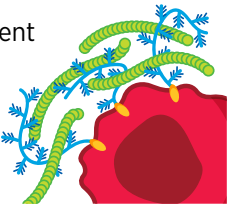
THE LYMPHATIC SYSTEM

Like blood vessels, the lymphatic system branches throughout the body and is essential for the immune system to function. This system is also responsible for maintaining fluid levels, removing waste, detecting pathogens, absorbing fats, and producing immune cells and antibodies in the lymph nodes. Tumor cells can manipulate the lymphatic system to grow new vessels that can transport cancer cells away from the primary tumor during metastasis (62). Changes in the way the lymph system grows have been observed in many cancers including melanoma, breast cancer, colorectal cancer, and squamous cell carcinoma of the head and neck (63). Ongoing efforts, including several clinical trials, are specifically focused on targeting lymph system growth in cancer (64).

THE IMMUNE SYSTEM

The immune system is composed of a variety of organs, tissues, cells, and molecules that work together to defend the body against external (virus, bacteria) and internal (cancer) threats by recognizing and eliminating them (see sidebars on **Cancer Growth: Local and Systemic Influences**, p. 25, and **Key Cells in the Immune System**, p. 26). Normally, cells that are precancerous and at risk of turning into cancer cells are eliminated by the immune system. However, certain cancer cells can manipulate the immune

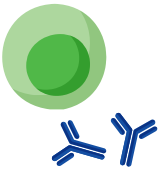
Tumors can manipulate collagen in the tumor microenvironment, creating barriers that prevent immune cells from getting to them (65). Collagen is the same protein that makes skin elastic and bones healthy.



Key Cells in the Immune System

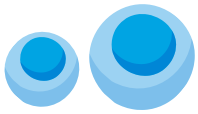
White blood cells are the cells of the immune system that work together to protect the body from pathogens and viruses. They can also cooperate to attack and destroy cancer cells. Here, we briefly describe the unique functions of the white blood cells that have a central role in eliminating cancer.

B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help the immune system function. Some remain as memory B cells to make the same antibody again later, if needed.



Macrophages eat foreign materials and can either help cancers grow or fight against progressing cancer cells.

CD4+ T cells help manage the immune response. Some remain as memory T cells to fight again later.

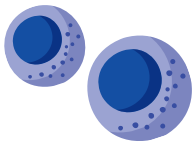


Dendritic cells educate T cells about what kinds of cells they should and should not attack.

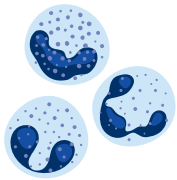
CD8+ T cells kill infected, damaged, and cancer cells. Some remain as memory T cells to fight again later.

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

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



Neutrophils, **basophils**, and **eosinophils** release chemicals against pathogens and stimulate the immune system.



Adapted from (8).

system so that they evade elimination. For instance, cancer cells can increase the amount of surface proteins that can put brakes on immune cells, effectively evading detection. Treatments that unleash the brakes on the body's immune system to fight cancer are called immunotherapies and these agents have drastically improved our ability to fight many types of cancer (see **Advances in Cancer Immunotherapy**, p. 87).

Ongoing research is likely to uncover additional mechanisms by which the immune system can be harnessed to eliminate cancer cells which may, in turn, lead to the development of new and improved treatments against cancer.

Cancer Development: Integrating Our Knowledge

The remarkable progress in discovery science during the past five decades has transformed our understanding of cancer. We have learned that cancer development is influenced by many factors, including a patient's biological characteristics, social and environmental exposures, and lifestyle. As each person's experience is unique, so is their cancer. As a result, we are now seeing a major shift from a "one size fits all" paradigm of cancer prevention, screening, and treatment to a more personalized approach called precision medicine.

Precision medicine aims to use genetic and other information about a patient's tumor, as well as other factors, to help diagnose, plan treatment, determine how well treatment is working, or make a prognosis, with the overarching goal of improving clinical outcomes and minimizing unnecessary diagnostic and therapeutic interventions.

Currently, a critical aspect of precision medicine is genetic sequencing of tumors to identify the specific mutations in the cancer cells so that therapies that are designed to target that mutation can be used. The effectiveness of this molecularly targeted strategy is becoming increasingly clear across a broad range of cancer types (see **Advances in Treatment with Molecularly Targeted Therapy**, p. 74) (66, 67). For instance, it has been shown that comprehensive genetic testing benefited individuals with rare cancers (i.e., diseases

The Cancer Genome Atlas, a National Institutes of Health (NIH)-supported **collaborative effort to genetically profile cancers**, is comprised mostly of samples from a majority of European ancestry patients (77 percent) despite this population only making up 59 percent of the population of the United States.

that affect fewer that 15 out of 100,000 people each year) by identifying treatment opportunities (68) (see **Adding Precision to the Treatment of Rare Cancers**, p. 74). Another study retrospectively sequenced the genomes of patients with cancer that were treated with immunotherapies to determine what mutations could be useful in predicting response. Based on common mutations in genes such as *KRAS*, *BRAF*, and *TP53*, researchers developed a model that predicted response to ICIs in treating metastatic cancers (69).

A clinical trial called the MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification (MAPPYACTS) performed comprehensive genomic testing of 787 recurrent or refractory malignances in AYA patients with cancer; this included sequencing DNA and RNA. Of this group, 436 patients had at least one genetic mutation identified that would benefit from an existing targeted treatment. Of this group, 30 percent went on to receive the matched therapeutic treatment leading to a response rate in half of those patients (70). Many studies are investigating how the use of tumor molecular profiling could identify targeted therapy opportunities for more patients with cancer (71).

Genetic sequencing of tumors using technologies such as next-generation sequencing is key to guiding precision medicine and has become more widely utilized in a variety of cancers. In 2019, approximately 40 perent of patients with advanced non-small cell lung cancer, metastatic colorectal cancer, metastatic breast cancer, and advanced melanoma had their tumors sequenced using next-generation sequencing technology, which increased from just one percent in 2011 (72). Unfortunately, tumor sequencing is not utilized by everyone despite the substantial benefits, with decreased likelihood of a patient being referred for a genetic test by a physician as well as lower rates of uptake observed for racial and ethnic minorities as well as those on Medicare (73-76). This necessitates increased and equitable access to genetic testing of tumors to maximize treatment potential and lessen unnecessary treatments (72,77).

Although genetic sequencing is a powerful tool for understanding changes in cancer cells that can guide treatment decisions, it is becoming increasingly clear that the influences and interactions of multiple additional factors including environmental, genetic, epigenetic, microbiome, and lifestyle factors must be understood for precision medicine to be most effective. More studies that look at these determinants of health from groups of different ancestral, racial, and ethnic backgrounds are necessary to build a better understanding of what leads to cancer. For instance, the All of Us research program launched by NIH in 2018 will enroll 1 million people in the United States to create a diverse database that includes data on biology, lifestyle, and environment and their effects on health. As of March 2022, this project had sequenced the entire genomes of 100,000 people, 50 percent of whom were racially or ethnically diverse. These types of databases will bring new knowledge to understanding the complex interactions that can lead to cancer and other diseases.

Preventing Cancer: Identifying Risk Factors

IN THIS SECTION YOU WILL LEARN:

- In the United States, four out of 10 cancer cases are associated with preventable risk factors.
- Not using tobacco is one of the most effective ways a person can prevent cancer from developing.
- Nearly 20 percent of U.S. cancer diagnoses are related to excess body weight, alcohol intake, poor diet, and physical inactivity.
- Many cases of skin cancer could be prevented by protecting the skin from ultraviolet radiation from the sun and indoor tanning devices.
- Nearly all cases of cervical cancer, as well as many cases of head and neck and anal cancers, could be prevented by HPV vaccination; many cases of liver cancer could be prevented by HBV vaccination.
- Decades of systemic inequities and social injustices have led to adverse differences in social determinants of health, causing a disproportionately higher burden of cancer risk factors among U.S. racial and ethnic minorities and other medically underserved populations.

Decades of research have led to the identification of numerous factors that increase the chance of developing cancer (**Figure 2**, p. 29). As a result of this work, we know that more than 40 percent of all cancer cases are attributable to preventable causes, including tobacco use, poor diet, physical inactivity, and obesity (78). In addition, vaccination against infection with the human papillomavirus (HPV) and hepatitis B virus (HBV) and decreasing exposure to ultraviolet (UV) radiation from the sun and indoor tanning devices can further reduce the burden of certain types of cancer. Identifying additional risk factors to enhance cancer prevention efforts is an area of intensive research (79).

Cancer risk factors such as tobacco use, poor nutrition, physical inactivity, and excessive alcohol use are also leading drivers of other chronic diseases, such as cardiovascular disease, respiratory diseases, fatty liver disease, and diabetes (80). Therefore, reducing or eliminating exposure to these factors through public education and policy initiative implementation has the potential to lessen the health and economic burden of many other diseases in addition to cancer.

In the United States, many of the greatest reductions in cancer morbidity and mortality have been achieved through the implementation of effective public education and policy initiatives. For example, the 32 percent decline in overall cancer mortality in the U.S. between 1991 and 2019 is largely attributed to reductions in smoking and advances in early detection for some cancers (1,81). Despite these advances, the prevalence of some of the major cancer risk factors continues to be high, particularly among segments of the U.S. population that experience cancer health disparities, such as racial and ethnic minorities and other medically underserved populations, as discussed in depth in the *AACR Cancer Disparities Progress Report 2022* (13).

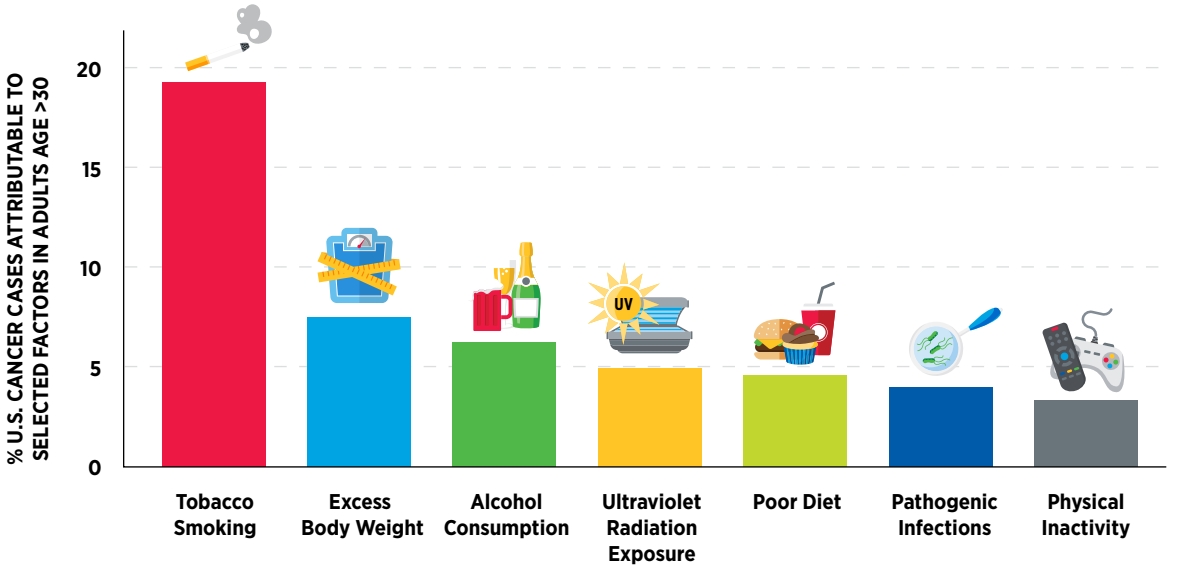
Disparities in the prevalence of preventable cancer risk factors stem from long-standing inequities in numerous social determinants of health among socioeconomically and geographically disadvantaged populations. Lifestyles, behaviors, and exposures are strongly influenced by living environments. For example, lack of quality housing (e.g., housing without smoke-free policies) may expose habitants to high levels of secondhand smoke, a known cause of lung cancer. Moreover, socioeconomically disadvantaged neighborhoods are often located in food deserts where there is reduced availability of healthy food options and an abundance of unhealthy, calorie dense, nutrient poor fast food, as well as limited outdoor space for recreation and/or exercise. These living environments create barriers to behaviors that are important in lowering cancer risk. It is imperative that all sectors work together to identify more effective strategies for reducing these barriers to healthy behaviors, disseminating our current knowledge of cancer prevention, and implementing evidence-based interventions to reduce the burden of cancer risks for everyone.

Eliminate Tobacco Use

Tobacco use is the leading preventable cause of cancer. Smoking is associated with the development of 17 different types of cancer in addition to lung cancer (see **Figure 3**, p. 30), because it exposes individuals to many harmful chemicals that cause cellular and molecular alterations leading to cancer development (82, 83). According to a recent analysis, adults who currently smoke have a three times greater risk of dying from cancer compared to those who do not smoke (84). Fortunately, smoking cessation at any age reduces the risk of

FIGURE 2

Increasing Cancer Risk



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

Adapted from (21).

cancer occurrence and cancer-related death (84). In addition, smoking cessation reduces risk for many adverse health effects beyond cancer, including cardiovascular disease and chronic obstructive pulmonary disease (85). Thus, one of the most effective ways a person can lower the possibility of developing cancer and other smoking-related conditions is to avoid or eliminate tobacco use.

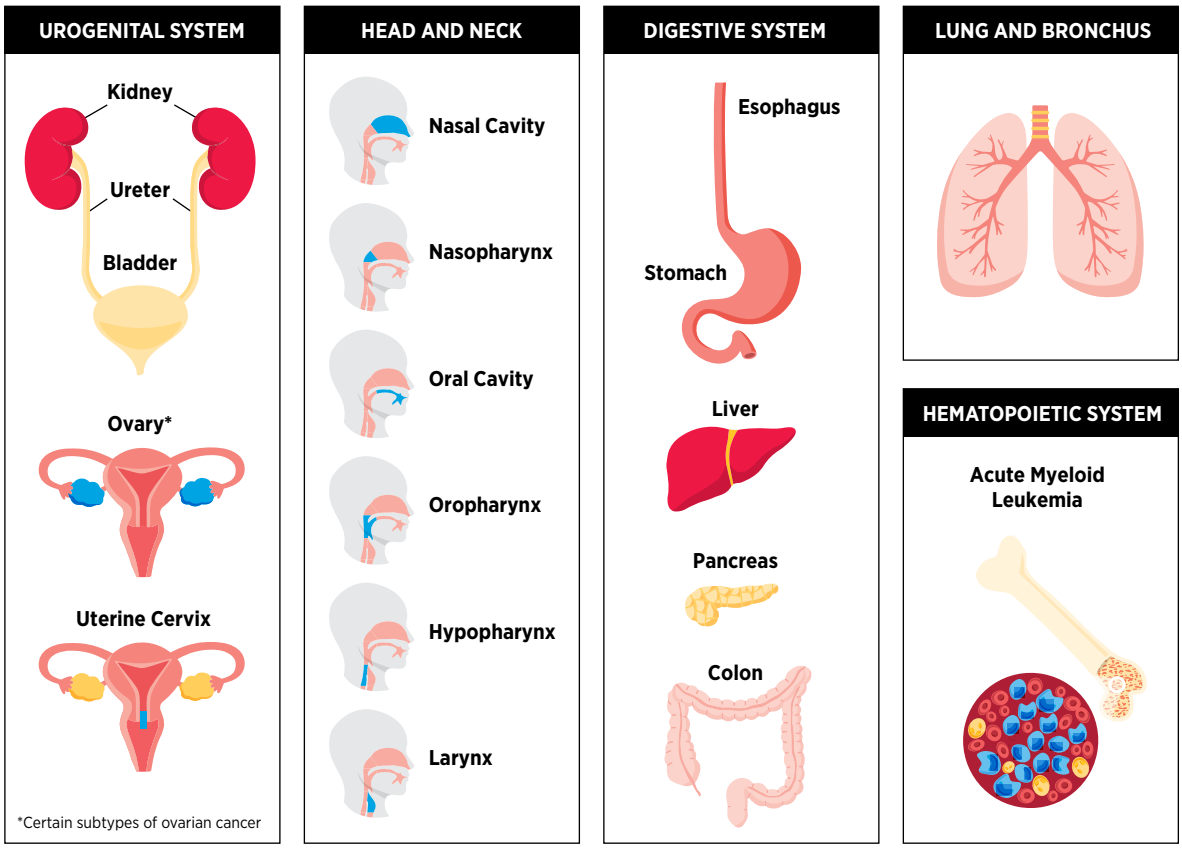
Thanks to the implementation of nationwide comprehensive tobacco control initiatives, cigarette smoking among U.S. adults has been declining steadily (86). In 2020, the most recent year for which such data are available, 12.5 percent of U.S. adults age 18 and older smoked cigarettes, a significant decline from 42.4 percent of adults in 1965, a year after the U.S. Surgeon General's landmark report on smoking was published (87,88). Exposure to secondhand smoke, which increases the risk of lung cancer among nonsmokers, has dropped substantially over the past three decades (89). Despite these positive trends, more than 47 million adults in the United States reported using a tobacco product in 2020 (87). Additionally, an estimated 5.2 million high school students and 1.3 million middle school students in the U.S. used some type of tobacco product in 2021 (90). These numbers are concerning because individuals who initiate smoking under the age of 17 have the highest risk of dying from cancer (84).

Evidence-based, local, state, and federal population-level interventions including tobacco price increases, public health campaigns, age and marketing restrictions, cessation counseling and FDA-approved medications, and smoke-free laws have the potential to further reduce smoking rates and smoking-related cancer burden in the United States (see **Leveraging Policy to Reduce Tobacco-related Illness**, p. 133). In this regard, researchers and policy makers are working in concert to evaluate strategies, such as increasing the federal cigarette tax or including graphic warning labels on packs of cigarettes, that may increase smoking cessation and reduce new smoking initiation (91,92).

The use of other combustible tobacco products (e.g., cigars), smokeless tobacco products (e.g., chewing tobacco and snuff), and waterpipes (e.g., hookahs) is also associated with adverse health outcomes including cancer (93). Electronic cigarettes (e-cigarettes) were introduced to the U.S. market almost 15 years ago and have gained enormous popularity among U.S. middle and high school students and young adults ages 18 to 24 (see sidebar on **E-Cigarettes: What Have We Learned and What Do We Need to Know?**, p. 32). The landscape of e-cigarette devices has evolved over the years to include different types of products such as prefilled pods (e.g., JUUL) or cartridge–based devices, and disposable (single use)

FIGURE 3

Beyond the Lungs: Cancers Caused by Smoking Tobacco



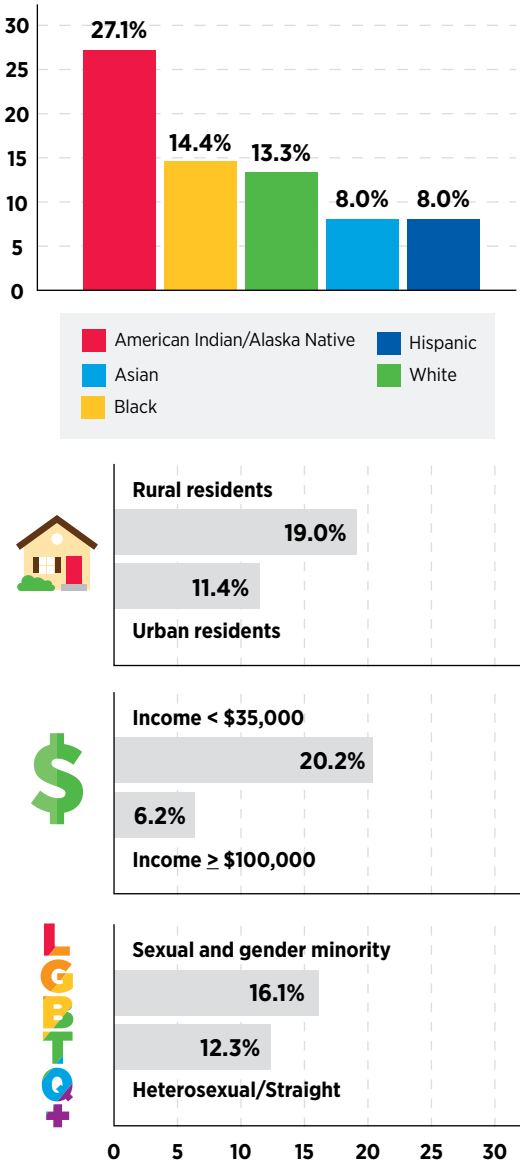
Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer. No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke. Use of smokeless tobacco (such as chewing tobacco and snuff) can cause oral, esophageal, and pancreatic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

Adapted from (21).

devices (e.g., Puff Bar), among others. E-cigarettes come in flavors that appeal to youth, and these flavors are key drivers of use among youth and young adults (94). E-cigarettes can deliver nicotine, an extremely addictive substance which is harmful to the developing brain, at similar levels as traditional cigarettes (95,96). While e-cigarettes emit fewer carcinogens than combustible tobacco, they still expose individuals to some toxic chemicals that can damage DNA and trigger inflammation (97-100).

After years of increase, the use of e-cigarettes declined among U.S. middle and high school students between 2019 and 2021 (21,101). These reductions may be attributed to an increased perception of harm from e-cigarettes as well as COVID-19-related factors such as having to stay at home, being afraid of parents finding out about e-cigarette use, and reduced access to e-cigarettes (111,112). However, more than 2 million middle and high school students still reported using e-cigarettes in 2021 (90). Clearly, more work needs to be done to effectively curb the use of these products in young populations. FDA has implemented several restrictions on e-cigarettes in the past year (see **Leveraging Policy to Reduce Tobacco-related Illness**, p. 133). It is imperative that all stakeholders continue to work together to determine the long-term health outcomes associated with e-cigarettes and identify new strategies to implement population-level regulations and reduce e-cigarette use among youth and young adults.

PERCENTAGE OF ADULTS AGE 18 AND OLDER WHO REPORTED CIGARETTE USE IN 2020 (87)



- **American Indian/Alaska Native (AI/AN) youth** are almost **twice as likely** to be frequent users of e-cigarettes as high school students overall (113).

- The U.S. Food and Drug Administration recently launched the **"Next Legends" youth e-cigarette prevention campaign**.
- **Through culturally tailored messaging**, the campaign will educate AI/AN youth, ages 12 to 17, about the harms of e-cigarette use.

In 2016, the **aggregate medical cost due to obesity among adults** in the United States was **$260.6 billion** (126).

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

Nearly 20 percent of new cancer cases and 16 percent of cancer deaths in U.S. adults are attributable to a combination of excess body weight, poor diet, physical inactivity, and alcohol consumption (78). Being overweight or obese as an adult increases a person's risk for 15 types of cancer; being physically active reduces risk for nine types of cancer (see **Figure 4**, p. 33). Therefore, maintaining a healthy weight, being physically active, and consuming a balanced diet are effective ways a person can lower the risk of developing or dying from cancer (see sidebar on **Ways to Reduce Cancer Risk**, p. 35). Identifying the underlying mechanisms by which obesity, unhealthy diet, and physical inactivity increase cancer risk and quantifying the magnitude of such risks are areas of active research.

The prevalence of obesity has been rising steadily in the United States. In 2020, 16 states had an adult obesity prevalence at or above 35 percent, up from nine states in 2018 and 12 in 2019 (122). Additionally, 22 percent of children and young adults ages 2 to 19 were considered obese, in 2020 (123). These data, however, may not fully reflect the impact of the COVID-19 pandemic, which has worsened obesity among most age groups (124,125).

There are significant sociodemographic disparities in the prevalence of obesity, driven largely by structural inequities and societal injustices (13,127). As one example, in 2019-2020, 16 percent of U.S. youth ages 10 to 17 were obese (127); the rates were higher among American Indian/Alaska Native youth (29 percent), non-Hispanic Black youth (24 percent), and Hispanic youth (21 percent) compared to non-Hispanic White youth (12

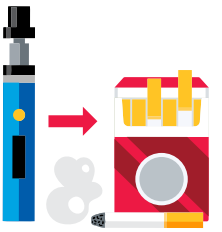
E-Cigarettes: What Have We Learned and What Do We Need to Know?

Electronic cigarettes (e-cigarettes) are battery-powered devices that provide nicotine, flavorings, and other additives to the user in the form of an aerosol. The vapor in electronic cigarettes is created by heating a flavored fluid (e-liquid) that is used inside e-cigarettes.

E-CIGARETTE CONSTITUENTS AND USERS' EXPOSURE TO HARMFUL CHEMICALS

- A single e-cigarette can deliver as much nicotine as a pack of combustible cigarettes.
- E-cigarettes are not harmless; in addition to nicotine, e-cigarettes contain and emit numerous potentially toxic substances including heavy metals, volatile organic compounds, tobacco-specific nitrosamines, aldehydes, phenolic compounds, and polycyclic aromatic hydrocarbons (94). Furthermore, e-cigarette aerosols contain numerous uncharacterized chemicals that might have health risks that are currently unknown (100).
- E-cigarettes expose individuals to carcinogens, but fewer than combustible tobacco (97).

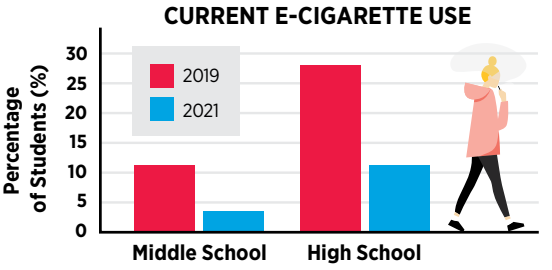
ROLE IN SMOKING CESSATION AND INITIATION



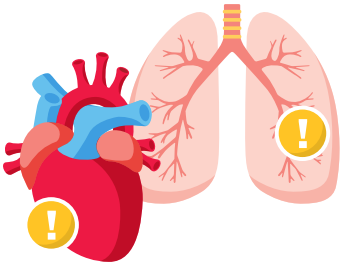
- FDA has not approved any e-cigarette as a cessation therapy. Only FDA-approved therapies like varenicline, nicotine replacement therapies, and counseling are demonstrated to improve chances of smoking cessation. E-cigarette manufacturers should follow FDA's regulatory pathways for cessation therapies by conducting clinical trials to assess the potential efficacy of helping smoking cessation.
- Individuals who stop using conventional cigarettes and switch to e-cigarettes have a higher risk of relapse compared to those who stop using all tobacco products (103).
- E-cigarette use increases the probability of youth or young adults transitioning to conventional cigarette use (104).

USE IN THE UNITED STATES

- Use is highest among youth (middle and high school students) and young adults (ages 18 to 24), and most young users prefer flavored e-cigarettes (90,101).
- Use among middle and high school students rose at an alarming rate between 2011 and 2019; of note, JUUL products comprised approximately 75 percent of the e-cigarette market in 2019 and were a major contributor to a doubling of youth e-cigarette use between 2017 and 2019 (102). Use has declined since.



ADVERSE HEALTH EFFECTS

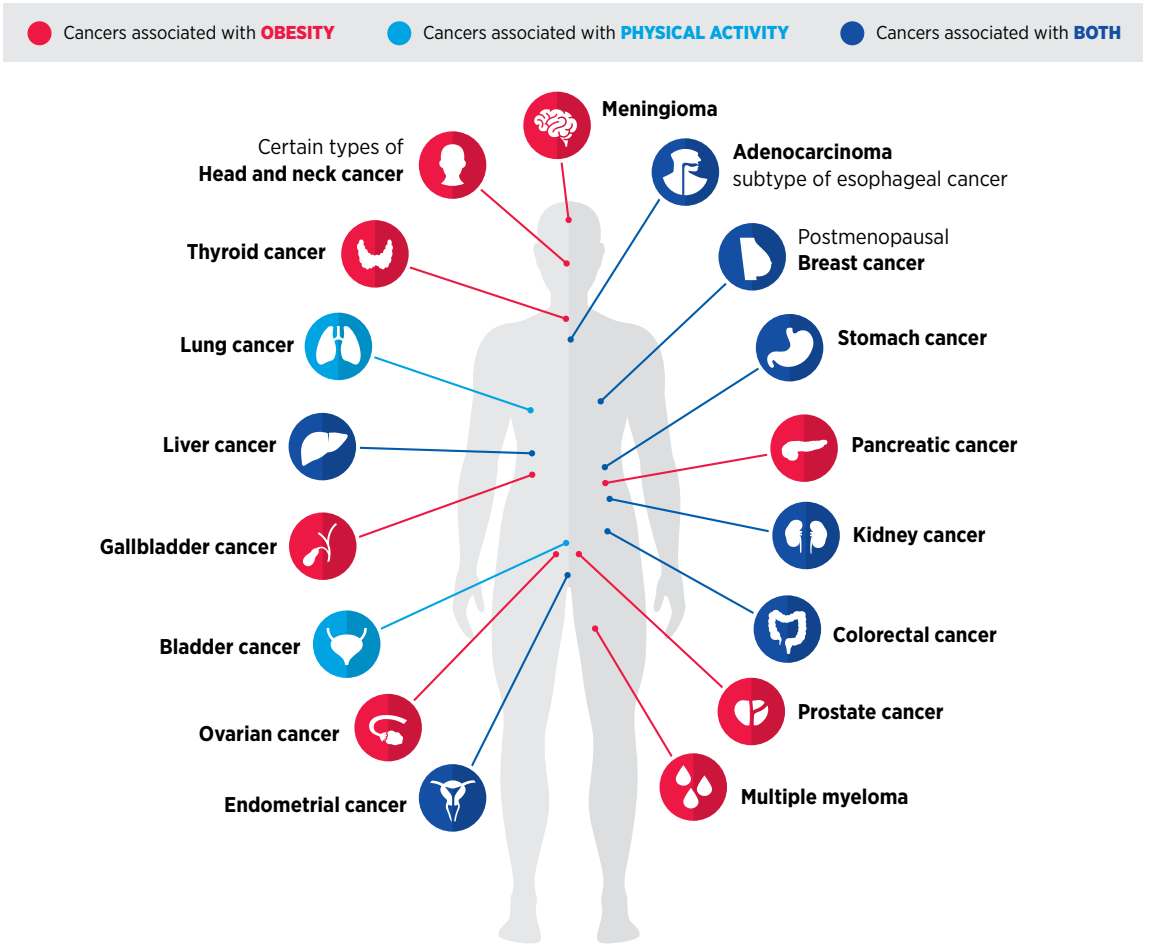


- Increasing evidence indicates that use of e-cigarettes can pose significant risks to vascular, respiratory, nervous system, and gastrointestinal health (105-108). Exposure to even a single session may have detrimental effects to the immune system (109).
- Preliminary data indicate that people who use both e-cigarettes and combustible cigarettes have similar levels of carcinogens in their urine as people who exclusively use combustible cigarettes (110).
- There is an urgent need for additional research to characterize definitively the long-term health risks, including cancer, cardiovascular and pulmonary diseases, and pregnancy outcomes.

Adapted from (21).

FIGURE 4

Reasons to Maintain a Healthy Weight and Stay Active

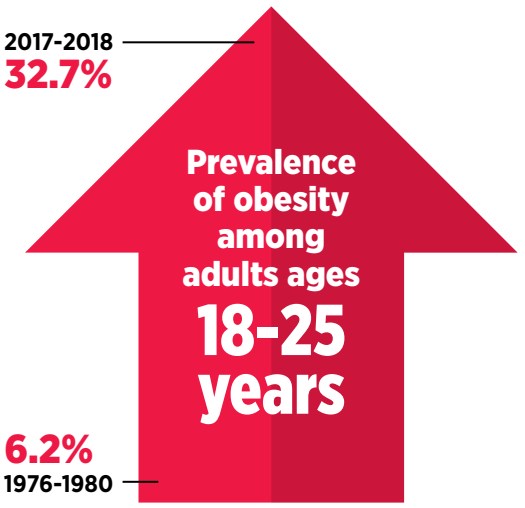


Fifteen types of cancer—the adenocarcinoma subtype of esophageal cancer; certain types of head and neck cancer; advanced prostate cancer; meningioma; multiple myeloma; and colon, rectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have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

Data from (114-120). Adapted from (121).

percent). It is important to address weight gain during early life since obesity during early childhood is associated with sustained overweight or obesity in adolescence and adulthood (128,129). There is also evidence that obesity during adolescence can increase the risk of developing cancer later in life (130).

Beyond cancer, obesity increases the risk of developing several other health problems including high blood pressure, heart disease, stroke, liver disease, kidney disease and type 2 diabetes which by itself is a risk factor for cancer (see **Reduce Risk of Diabetes**, p. 42).



Source: (131)

Emerging data indicate that weight loss intervention through bariatric surgery may lower the future risk of certain obesity-related cancers (132,133). According to a recent study, among adults with obesity, bariatric surgery compared to no surgery was associated with a 32 percent reduction in obesity-associated cancer incidence and 48 percent reduction in cancer-related mortality (134). While further research is needed to elucidate whether weight loss can effectively mitigate risks of developing and/or dying from all obesity-related cancers, identifying equitable strategies including lifestyle and therapeutic interventions to address obesity must certainly be a top priority among U.S. public health efforts.

Complex and interrelated issues ranging from health literacy and other socioeconomic factors, to environmental, biological, and individual lifestyle factors may contribute to obesity; there is, however, sufficient evidence that consumption of high-calorie, energy-dense foods and beverages and lack of physical activity play a significant role in obesity (127). To achieve and maintain good health, U.S. Departments of Agriculture and Health and Human Services, in *Dietary Guidelines for Americans, 2020-2025*, recommend that individuals follow a healthy dietary pattern at every stage of life (136). According to the guidelines, all individuals should fulfill their nutritional needs by consuming nutrient-dense food and beverages including fruits, vegetables, whole grains, low-fat dairy products, lean meat, eggs, seafood, beans, legumes, nuts, and vegetable oil, and limit foods and beverages that are high in added sugars, saturated fat, and sodium, as well as alcoholic beverages (136).

In the United States, more than five percent of all newly diagnosed cancer cases among adults are attributable to eating a poor diet (137). Based on recent data, in 2019, only 12 percent and 10 percent of U.S. adults met their fruit and vegetable intake recommendations, respectively (138). High intake of highly processed foods contributes to obesity. Therefore, it is concerning that among U.S. children and youth ages 2 to 19 years, the estimated percentage of total energy consumed from highly processed foods increased from 61 percent to 67 percent between 1999 and 2018 (139).

There are significant disparities in diet quality among different segments of the U.S. population attributable largely to socioeconomic and geographic factors. Based on a recent report, individuals who are Black, have low education, or live in rural areas and food deserts—neighborhoods that lack access to healthy food retail such as supermarkets, and have an overabundance of unhealthy and fast-food options—are more likely to have poor diet quality (140). In contrast, higher access to grocery stores, lower access to fast food, higher income and college education are associated with eating healthily and maintaining a healthy weight (141). These findings underscore the necessity for public policies to increase access to affordable nutritious food, as well as the need for educational interventions to improve nutritional knowledge for everyone, specifically among medically underserved populations.

A major barrier to healthy diet is food insecurity, defined by the U.S. Department of Agriculture (USDA) as the lack of access by all people in a household at all times to enough food for an active, healthy life. Many studies have found an association between food insecurity and excess body weight (127). Researchers have hypothesized several mechanisms by which food insecurity may lead to obesity, including increased consumption of unhealthy diet, stress and anxiety generating higher levels of stress hormones, which heighten appetite, and a physiological response to reduced food availability leading to higher fat storage in the body (127).

One initiative that has been effective in increasing the consumption of healthy food and lowering the rates of obesity among children from low-income families is the Special Supplemental Nutrition Program for Women, Infants, and Children (143,144). Additionally, a program (SuperSNAP) that provides additional funds to Supplemental Nutrition Assistance Program beneficiaries for purchase of fruits and vegetables was recently shown to be associated with significant increases in healthy food purchasing (145). While ongoing research needs to evaluate the long-term health outcomes of this program, incentives like SuperSNAP are vital, especially for populations that experience food insecurity.

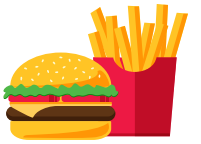
A 40-year-old could **add a decade to his or her life expectancy** by switching from a typical Western diet to one that includes **more legumes, whole grains, and nuts, and less red and processed meat** (142).

Ways to Reduce Cancer Risk

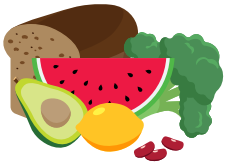
Research shows that about one-fifth of all cancers diagnosed in the United States are attributable to being overweight or obese, being physically inactive, eating poorly, and drinking excessively. Based on current evidence, public health experts recommend that people:

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

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



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



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

Be physically active as part of everyday life because regular physical activity can decrease risk for nine types of cancer (see sidebar on **Physical Activity Guidelines**, p. 36 for details).

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

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

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

Greater adherence to these recommendations has been shown to be associated with a reduced risk of all-cause, cancer-specific, and cardiovascular disease-related mortality among adults ages 50 to 71 (135).

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

Adapted from (13).

Research indicates that over 46,000 U.S. cancer cases annually could potentially be avoided if everyone met the recommended physical activity guidelines (see sidebar on **Physical Activity Guidelines**, p. 36) (146). Engaging in recommended levels of physical activity can lower the risks for developing nine types of cancer (see **Figure 4**, p. 33), and emerging evidence indicates that there may be risk reduction for even more cancer types (115-117). In addition to cancer, muscle-strengthening and aerobic activities can also lower the risk of all-cause mortality, cardiovascular disease, and diabetes (147). According to a recent study in U.S. adults, an additional 20 minutes of exercise a day could prevent nearly 210,000 deaths each year (148). Unfortunately, according to

Middle-aged adults taking at least **7,000 steps per day** have a greater than **50 percent lower risk of all-cause mortality** compared to those taking fewer than 7,000 steps per day (150).

Physical Activity Guidelines

The U.S. Department of Health and Human Services recommends the following minimum physical activity levels to improve the nation's health:

FOR PRESCHOOL-AGE CHILDREN

- Physical activity throughout the day to enhance growth and development
- Three hours per day of activity of all intensities

FOR SCHOOL-AGE CHILDREN AND ADOLESCENTS

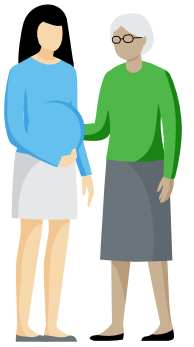
- Sixty minutes or more of physical activity (for example, running) daily
- Muscle- and bone-strengthening exercises such as push-ups at least three days per week

FOR ADULTS

- All adults should avoid inactivity; some physical activity is better than none.
- At least 150 minutes per week of moderate-intensity activity such as a brisk walk or 75 minutes per week of vigorous-intensity activity such as running
- Moderate- or high-intensity muscle-strengthening activities two or more days per week

FOR SPECIFIC POPULATIONS

- Older adults, those who are pregnant, and/or those with chronic health conditions and disabilities should consult their physicians and follow modified guidelines
- Cancer survivors should consult their physicians and follow modified guidelines adapted for their specific cancers and treatment



Adapted from (21).

a current report, only 35 percent of men and 27 percent of women age 18 and older in the U.S. met the federal guideline for muscle-strengthening physical activity in 2020 (149).

There are also striking sociodemographic disparities among those who are physically active, with a higher prevalence of activity recorded among adults who are White, have a college education, have higher income, and have private health insurance (151). Living in low-income neighborhoods, which are more likely to lack safe and affordable options for physical exercise, such as gyms, biking and hiking trails, and biking and walking paths, contributes to such disparities. It is imperative that health care professionals and policy makers work together to increase awareness of the benefits of physical activity and support programs and policies that facilitate an active lifestyle for everyone along their lifespan.

Limit Alcohol Consumption

Alcohol consumption increases the risk for six different types of cancer (152) (see **Figure 5**, p. 37), and emerging evidence indicates that there may be increased risks for additional cancer types (153). Even modest intake of alcohol may increase cancer risk, but the greatest risks are associated with excessive and/or long-term consumption (154-156) (see sidebar on **Guidelines for Alcohol Consumption**, p. 38). Research indicates that excessive drinking during early adulthood might increase cancer risk later in life even if drinking stops or decreases in middle age (157). Notably, according to a recent global analysis, among individuals consuming harmful amounts of alcohol in 2020, nearly 60 percent were ages 15 to 39 years (158).

In the United States, alcohol consumption accounted for greater than 75,000 cancer cases and nearly 19,000 cancer

One in six U.S. adults reported **binge drinking** during the **past 30 days** in 2018 (163)

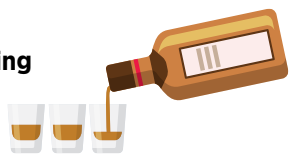
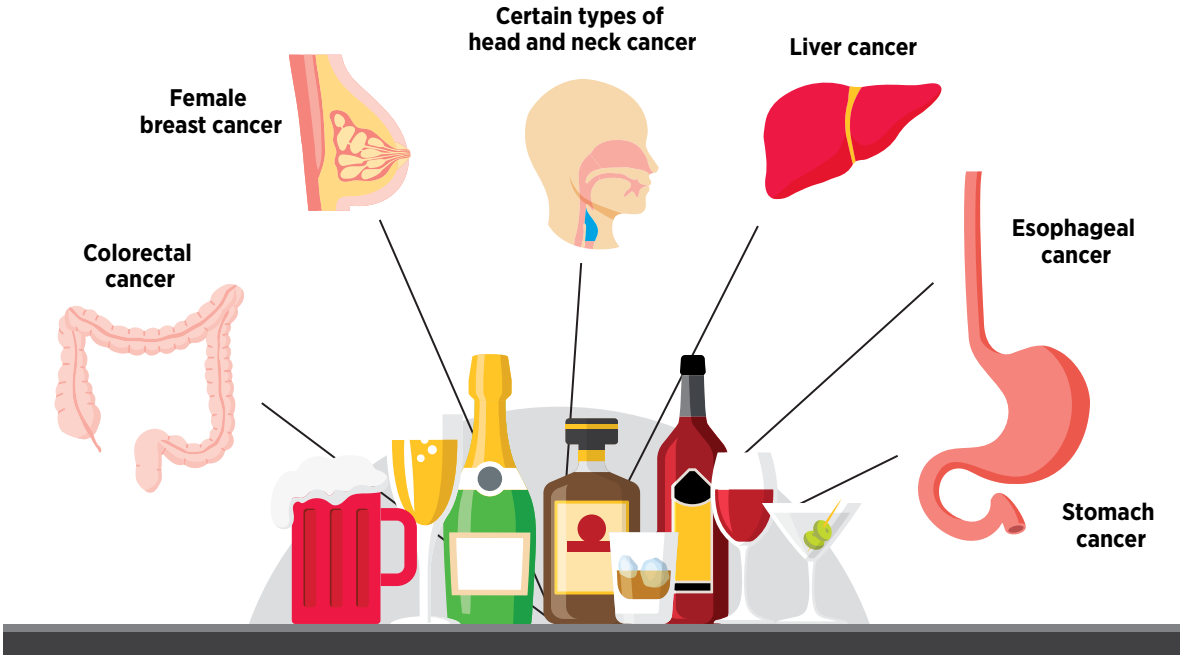


FIGURE 5

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.

deaths annually between 2013 and 2016 (159). Consumption of alcohol varies by sociodemographics and is higher among men with lower education and lower income compared to men who are college graduates and have higher income, as well as among certain sexual and gender minority populations (160). There are concerns that the COVID-19 pandemic has further increased alcohol use (161,162). These data underscore the importance of adhering to comprehensive guidelines to limit and/or eliminate alcohol intake and minimize the risk of developing a disease or dying due to alcohol.

Future efforts focused on evidence-based policy interventions, such as regulating alcohol retail density, taxes, and prices, as well as public education (e.g., cancer-specific warning labels displayed on alcoholic beverages), need to be implemented along with effective clinical strategies to reduce the burden of alcohol-related cancers. In this regard, a recent survey indicated that nearly 65 percent of U.S. citizens support adding warning labels and drinking guidelines to alcohol containers (164). Notably, awareness among survey respondents of the risks of cancer from alcohol consumption was associated with a greater support of warning labels indicating that increasing public awareness of the alcohol–cancer link may increase support for alcohol control policies. Increasing public awareness of the harmful effects of alcohol is important in light of data from a recent survey that indicate only 31 percent of Americans recognize alcohol is a risk factor for cancer (165).

Protect Skin from UV Exposure

Exposure to UV radiation from the sun or indoor tanning devices poses a serious threat for the development of the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma, the latter being the deadliest form of skin cancer. Overall, exposure to UV light accounts for four to six percent of all

In 2019, **5.7 percent of female adolescents** used an **indoor tanning device** within the past year (176).

Guidelines for Alcohol Consumption

The U.S. Department of Agriculture and U.S. Department of Health and Human Services, *Dietary Guidelines for Americans, 2020-2025*, recommends (136):

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**.

One drink is described as containing **14 g (0.6 fl oz) of pure alcohol**.

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

12 fl oz of regular beer (5% alcohol)

5 fl oz of wine (12% alcohol)

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

According to the National Institute on Alcohol Abuse and Alcoholism:

HEAVY DRINKING

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

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

BINGE DRINKING

≥ 4 drinks within 2 hours for women

≥ 5 drinks within 2 hours for men

Excessive alcohol consumption includes binge drinking, heavy drinking, and any drinking by pregnant women or those under 21 years of age.

Adapted from (21).

cancers and is responsible for 95 percent of skin melanomas (78). Thus, one of the most effective ways a person can reduce the risk of skin cancer is by practicing sun-safe habits and not using UV indoor tanning devices (see sidebar on **Ways to Protect Your Skin**, p. 39).

In the United States, melanoma incidence has been rising for decades. Based on a new analysis, during 2009 to 2018, incidence of malignant melanoma of the skin increased by an average of 1.2 percent per year (166). Public education regarding skin cancer risk reduction is extremely important considering findings from many recent surveys conducted in the U.S. indicate a lack of understanding of skin cancer and sun protection and high incidence of sunburns among participants (2021) (167). In addition, there are disparities in the level of knowledge about the dangers of sun exposure and importance of using sunscreen, with Black and Hispanic individuals reporting less knowledge and being less likely to use sunscreen compared to White individuals (168,169).

Use of indoor UV tanning devices increases a person's risk for melanoma. One population with a high prevalence of indoor tanning is sexual minority men compared to heterosexual men (170,171). Sexual minority men are also more likely than heterosexual men to report having skin cancer (171). Laws prohibiting tanning can be effective in reducing tanning practices and may reduce the incidence of future melanoma cases and associated health care costs (172-174). However, as of January 1, 2021, in the U.S., only 20 states and the District of Columbia have laws prohibiting tanning for minors (under the age of 18) (175). It is vital that all stakeholders in public health continue to work together to develop and implement more effective policy changes and public education campaigns to reduce the practice of indoor tanning, especially among high-risk populations.

Prevent and Eliminate Infection with Cancer-causing Pathogens

Persistent infection with several pathogens—disease-causing bacteria, viruses, and parasites—increases a person's risk

Ways to Protect Your Skin

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

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

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

Wear a **wide-brimmed hat**.

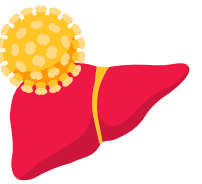
Wear **wrap-around sunglasses**.

Apply the recommended amount of a sunscreen before going outside (even on slightly cloudy or cool days); **use sunscreen that provides protection against UVA and UVB rays** and that is rated sun protection factor **(SPF) 15 or higher**, at least every 2 hours and after swimming, sweating, and toweling off.

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

Adapted from (21).

Hepatitis B virus can trigger genetic changes in liver cells years or even decades before a cancer is diagnosed (186).



for several types of cancer (see **Table 3**, p. 40). In the United States, about three percent of all cancer cases are attributable to infection with pathogens (78). Globally, an estimated 13 percent 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* (177,178).

Individuals can significantly lower their risks by protecting themselves from infection or by seeking treatment, if available, to eliminate an infection (see sidebar on **Ways to Reduce Cancer Risk from Pathogens**, p. 41). It is important to note that even though strategies to eliminate, treat, or prevent infection with *Helicobacter pylori*, HBV, HCV, and HPV can significantly lower an individual's risks for developing cancers, these strategies are not effective at treating infection-related cancers once they develop.

Chronic infection with HBV and HCV can cause liver cancer and is increasingly recognized as a risk factor for additional malignancies such as non-Hodgkin lymphoma (179,180). Unfortunately, after decades of decline, the number of new HBV infections is now rising among adults age 40 and older, despite the availability of a safe and effective vaccine (181). As a result, CDC recently recommended that all adults ages 19 to 59 years receive a vaccination for HBV (182). Current evidence shows significant gaps in the perception and treatment of HBV, especially among racial and ethnic minorities, highlighting the need for community-based, culturally appropriate interventions to mitigate the disparate burden of the virus (183,184). Acute infection with HCV is often asymptomatic but more than half of these cases progress to chronic infection. The rate of reported acute HCV cases in the United States increased by 89 percent between 2014 and 2019, with the highest rate among AI/AN persons (185).

To eliminate viral hepatitis as a public health threat, the U.S. Department of Health and Human Services recently released the *Viral Hepatitis National Strategic Plan for the United States: A Roadmap to Elimination (2021–2025)* (187). The primary goals listed in the report are to prevent new infections, improve hepatitis-related health outcomes for infected individuals, reduce disparities and health inequities related to hepatitis, improve surveillance of viral hepatitis, and bring together all relevant stakeholders in coordinating efforts to address the hepatitis epidemic.

Persistent infection with HPV is responsible for almost all cervical cancers, 90 percent of anal cancers, about 70 percent of oropharyngeal cancers, and more than half of all vaginal, vulvar, and penile cancers (188). This knowledge has driven the development of vaccines that prevent infection with some cancer-causing strains of HPV and the development of a clinical test that detects cancer-causing HPV strains in cervical cells. There are 13 different types of HPV that can cause cancers; the HPV vaccine currently used in the United States, Gardasil 9, can protect against nine of these HPV strains (see sidebar on **HPV Vaccination Recommendations**, p. 42) (188).

There is emerging evidence affirming that the receipt of guideline-concordant HPV vaccination significantly lowers the risk of infection with HPV types that are covered by

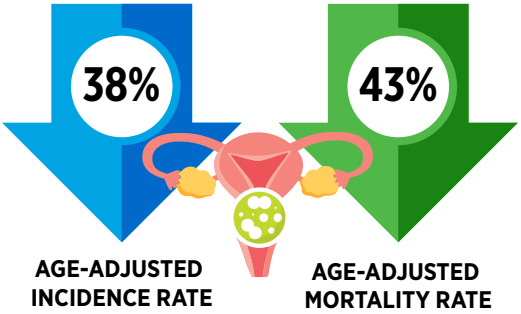
TABLE 3

Cancer-causing Pathogens

Bacteria		
Pathogen	**Cancer types caused by the pathogen**	**Number of global cancer cases**
Helicobacter pylori	Stomach cancer and non-Hodgkin lymphoma	810,000
Parasites		
Pathogen	**Cancer types caused by the pathogen**	**Number of global cancer cases**
Clonorchis sinensis and Opisthorchis viverrini	Cholangiocarcinoma	3,500
Schistosoma haematobium	Bladder cancer	N/A
Virus		
Pathogen	**Cancer types caused by the pathogen**	**Number of global cancer cases**
Epstein-Barr Virus (EBV)	Hodgkin lymphoma, certain types of non-Hodgkin lymphoma, and nasopharyngeal cancer	156,600
Hepatitis B Virus (HBV)	Hepatocellular carcinoma and other cancers	360,000
Hepatitis C Virus (HCV)	Hepatocellular carcinoma and other cancers	156,000
Human Herpes Virus type-8 (HHV-8; also known as Kaposi sarcoma herpes virus)	Kaposi sarcoma	42,000
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	N/A
Human Papillomavirus (HPV)	Anal, cervical, head and neck, larynx, oral, oropharyngeal, penile, vaginal, and vulvar cancers	690,000
Human T-cell Lymphotrophic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma	3,600
Merkel Cell Polyomavirus (MCV)	Skin cancer	N/A

Data from https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(19)30488-7/fulltext

Rates of cervical cancer incidence and mortality have declined among **U.S. women ages 15 to 24** between **2001-2005** (pre-HPV vaccination) and **2010-2017** (postvaccination).

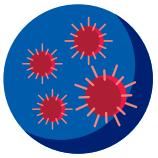
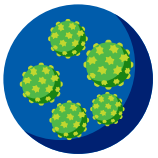


Source: (192)

the vaccines and dramatically reduces the incidence of and mortality from cervical cancers among the vaccinated (189-192). According to a recent analysis, prior to the HPV vaccination approval, cervical cancer rates among 20- to 24-year-old U.S. women were decreasing at 2.3 percent annually during 2001 and 2011; after the vaccine approval, these rates decreased at 9.5 percent per year during 2011 and 2017 (190). Additionally, recent findings suggest that the incidence of certain anal cancers has decreased among vaccine-eligible individuals ages 20 to 44 between 2009 and 2018 (193).

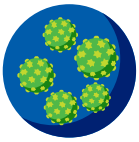
Despite the positive impacts, the uptake of HPV vaccines has been suboptimal in the United States. While there has been some progress in recent years, only 56 percent of boys and 61 percent of girls who are eligible were up to date on their vaccination regimen in 2020 (194). These numbers stand in sharp contrast to those from the United Kingdom where high uptake of HPV vaccination among 12 to 13-year-old girls, since the onset of the program in 2008, has nearly eliminated cervical cancer in women born since September 1995 (191).

Ways to Reduce Cancer Risk from Pathogens

PATHOGEN	WAYS TO PREVENT INFECTION	WAYS TO ELIMINATE OR TREAT INFECTION	U.S. 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 has been part of the childhood immunization schedule since 1991. In March 2022, CDC updated its recommendation suggesting all adults ages 19 to 59 years receive a vaccination. • CDC and USPSTF recommend screening high-risk individuals—those from countries with high rates of HBV infection, HIV-positive persons, injection drug users, household contacts of HBV-infected individuals, and men who have sex with men—for HBV infection
Hepatitis C virus (HCV) 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment with any of several antiviral drugs can eliminate infection	There is consensus in recommendations from CDC and USPSTF for universal screening of all adults ages 18 to 79.
Human papillomavirus (HPV) 	• Three FDA-approved vaccines • Practice safe sex, although this may not fully protect against infection	None available	CDC recommends HPV vaccination for boys and girls age 11 or 12; recommendations for other groups can be found in sidebar on **HPV Vaccination Recommendations**, p. 42)

CDC, Centers for Disease Control and Prevention; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force.
Adapted from (21).

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.

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.

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

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

Adapted from (21).

Women who received the HPV vaccine at ages 12 to 13 had an 87 percent **lower risk of contracting cervical cancer** compared to those who were unvaccinated (191).

Until recently, cervical cancer was the most common HPV-related cancer in the United States. However, the incidence of HPV-related oropharyngeal and anal cancers has been increasing and oropharyngeal squamous cell carcinoma was recently reported to have become the most common HPV-associated cancer in the United States. Therefore, developing effective strategies to improve the uptake of HPV vaccines could have immense public health benefits.

All stakeholders must work together and develop better strategies to increase the uptake of HPV vaccination in the United States. These include ensuring that health care providers recommend HPV vaccination to all eligible adolescents and their parents, improving provider-parent communication, increasing parental awareness, and removing structural and financial barriers to increase access to vaccination. In this regard, there is new evidence that a single dose of the HPV vaccine may protect against cancer-causing infections (196,197). Giving just one HPV vaccine dose instead of multiple doses, as is currently recommended, can potentially reduce the cost and simplify the logistics of vaccination, increasing the overall uptake, particularly in low-resource settings. Additionally, there is a vital need for increased public education to enhance trust in vaccination considering recent evidence that hesitancy related to the HPV vaccine has increased among parents (198).

Reduce Risk of Diabetes

Diabetes is a chronic health condition that affects how food is converted into energy. There are three main types, type 1, type 2, and gestational diabetes. In healthy individuals, food is broken down into sugar, also called glucose, which is released into the bloodstream and taken up by cells for use as energy through the help of the molecule insulin. Individuals with diabetes do not make enough insulin or cannot efficiently use the insulin the

THERE ARE THREE MAIN TYPES OF DIABETES:

Type 1 diabetes

When a person's immune system attacks and destroys the cells in the body that make insulin. Five to 10 percent of those who have diabetes have type 1.

Type 2 diabetes

When a person's body does not make or use insulin well. Ninety to 95 percent of people with diabetes have type 2.

Gestational diabetes

When a person's body does not make enough insulin during pregnancy.

body makes. Lack of enough insulin leads to excessive blood sugar levels that can cause serious health problems, such as heart disease, vision loss, and kidney disease. Researchers have found that individuals with both type 1 and type 2 diabetes are at an increased risk of developing certain types of cancer such as liver, pancreatic, endometrial, colorectal, breast, and bladder cancer (199). Ongoing studies are evaluating the risks for other cancer types (200,201). Additionally, there is evidence that diabetes may be associated with increased mortality from cancer (200).

In the U.S. 37.3 million people have diabetes. Unfortunately, one of five individuals is unaware of having the condition (202). There are also disparities in the burden of diabetes. In the U.S., prevalence is higher among Black and Hispanic populations compared to the White population (203).

Diabetes (type 2) and cancer share several nonmodifiable and modifiable risk factors such as aging, obesity, poor diet, physical inactivity, and smoking. While the increased risk for cancer may be explained, in part, by the shared risk factors, researchers have uncovered potential mechanisms that may explain a direct link between diabetes and cancer. These include diabetes-associated inflammation and high levels of insulin and glucose, all of which have been independently linked with cancer development (204). Identifying the exact mechanisms by which diabetes increases cancer risk and targeting those pathways to reduce risks are areas of extensive research.

Fortunately, there are many ways in which individuals with diabetes can lower their cancer risk. Keeping blood sugar levels under control and avoiding hyperglycemia are key to risk reduction. People with diabetes can lower their risk of cancer by adopting a healthy lifestyle. Eating a healthful diet rich with vegetables, fruits, and whole grains, engaging in regular physical activity, limiting alcohol consumption, and eliminating tobacco use may significantly reduce the risk of diabetes and cancer. It is important that patients with diabetes be aware of their increased cancer risk and undergo recommended age- and sex-appropriate cancer screenings (205).

Be Cognizant of Reproductive and Hormonal Influences

PREGNANCY AND BREASTFEEDING

Historically, parous women—women who have given birth—were known to be less likely to develop breast cancer than nulliparous women—women who have not given birth—due to the protective effect of pregnancy. However, in the last five decades, there has been a substantial increase in age at first pregnancy and reduction in the number of children women have, leading to the uncovering of differential effects of pregnancy on breast cancer. Importantly, recent studies have shown that giving birth reduces the risk in mothers for developing a common type of breast cancer, known as estrogen receptor-positive tumor (206-208). Notably, the risk reduction in breast cancer incidence is manifested only after a decade or longer following a woman's last pregnancy, with greater protection conferred with increasing time (206,208). The net result is that parous women are at reduced risk for developing breast cancer after menopause (when most breast cancers are diagnosed) compared to their nulliparous peers. Further research is needed to understand this protective mechanism.

In contrast, during the five to ten years after giving birth, referred to as the postpartum period, women face an elevated risk for breast cancer diagnosis compared to those who have never given birth (206,208). Because these cancers occur in young, mostly premenopausal women, they are referred to as early-onset breast cancers. Further, recent childbirth associates with increased risk for estrogen receptor-negative tumors, an intractable form of breast cancer (209). Overall, young women are at a higher risk of developing triple-negative breast cancer and this risk increases soon after childbirth, but then attenuates with time (206,208,209). Thus, for young women, a recent childbirth increases the risk of early onset breast cancer, particularly poor prognostic estrogen receptor negative cancers.

Recent data indicate that breast cancers arising in young women during postpartum period, referred to as postpartum breast cancers, are associated with an increased risk for metastasis and worse outcomes compared to breast cancers diagnosed in young, premenopausal women who have not given birth (210-213). Even early-stage, estrogen receptor-positive breast cancers, which otherwise have favorable prognosis, have poor outcomes when diagnosed as postpartum breast cancer, and poor prognostic gene expression signature (214,215). Research has also shown that breast cancers occurring during pregnancy have different biological characteristics and better prognosis compared to those that are diagnosed during the postpartum period (216,217). Identifying interventions that may alleviate the tumor-promoting potential of recent childbirth, as well as best therapeutic options to treat postpartum breast cancers are areas of extensive investigation (218).

There is evidence that breastfeeding can be protective against breast cancer development in mothers (219-221). Emerging data suggest that breastfeeding may also be associated with a lower risk of ovarian cancer development (222,223). These protective effects have been described in both Black and White women (208,219,224,225). Based on current evidence, breastfeeding reduces the increased risk of estrogen receptor-negative cancers that is associated with having children. Notably, the increased risk of triple-negative breast cancer diagnosis associated with giving birth can be reduced by breastfeeding, with longer durations of breastfeeding further decreasing the risk (118,208,219,224-226). Studies have shown that breastfeeding decreases the risk of triple-negative breast cancers for younger Black women (219,224,227). Unfortunately, the awareness of the benefits of breastfeeding in reducing cancer risk is low among U.S. women (228). Culturally tailored public education and public health policies in support of lactation are needed, specifically for medically underserved populations, such as young Black women, who have a disproportionately higher incidence of triple-negative breast cancer, and a lower prevalence of breastfeeding compared to all other U.S. racial and ethnic groups (229-230).

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) refers to treatments that aim to relieve the common symptoms of menopause and the long-term biological changes, such as bone loss, that take place after menopause. These changes occur due to the decline in the levels of the hormones estrogen and progesterone, in a woman's body. HRT usually involves treatment with estrogen alone or estrogen in combination with progestin, a synthetic hormone similar to progesterone. Women who have a uterus are prescribed the estrogen and progestin combination. This is because estrogen alone, but not in combination with progestin, is associated with an increased risk of endometrial cancer, a type of cancer that forms in the tissue lining the uterus. Estrogen alone is used only in women who have had their uteruses removed.

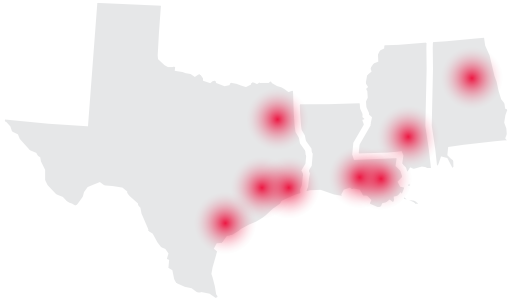
Comprehensive evidence about the health effects of HRT was obtained from clinical trials conducted by NIH as part of the Women's Health Initiative (WHI). The data indicated that women who use the estrogen and progestin combination have an increased risk of developing breast cancer (231,232). The risk is greater with longer duration of use and is nearly two fold higher among women who have used estrogen plus progestin combination for 10 years or longer compared to those who never used HRT (233-235). 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 (234). More recently, analyses from the United Kingdom have corroborated the data from WHI and showed that long-term use of the estrogen and progestin combination is associated with an increase in the risk of breast cancer (236,237). Individuals who are seeking relief from menopausal symptoms should discuss with their health care providers the advantages and possible risks of using HRT before deciding what is right for them.

Another area of ongoing investigation in exogenous hormone use is the differential cancer risks among individuals undergoing gender-affirming hormonal therapy (238). While current data is very limited, there is emerging evidence indicating an increased risk of breast cancer but a lower risk of prostate cancer among trans women who received gender-affirming hormonal therapy compared to age-matched cisgender men and a lower risk of breast cancer in trans men who received gender-affirming hormonal therapy compared to age-matched cisgender women (239,240). Long-term, longitudinal, population-based studies are needed to comprehensively assess the risk of cancers in these understudied and medically underserved populations.

Limit Exposure to Environmental Risk Factors

Environmental exposures to pollutants and certain occupational agents can increase a person's risk of cancer. For example, radon, a naturally occurring radioactive gas that comes from the breakdown of uranium in soil, rock, and water, is the leading cause of U.S. lung cancer deaths among never smokers albeit levels of naturally occurring radon vary widely based on geographic location within the country (175,241). Other examples of environmental carcinogens include arsenic, asbestos, lead, radiation, and benzene (242). According to the World Health Organization (WHO), environmental risk factors account for nearly 20 percent of all cancers globally, most of which occur in low- and middle-income countries.

Data from a **U.S. Environmental Protection Agency (EPA)-based model called Risk-Screening Environmental Indicators** were used in a recent effort to create a detailed map to **visualize the cumulative cancer risk from toxic industrial air pollution** across the United States. The map identified many cancer "hot spots"—areas where the added cancer risk due to toxic air pollution over a lifetime averaged for five years is at or above 1 in 100,000 (243).



It can be difficult for people to avoid or reduce their exposure to environmental carcinogens, and like behavioral and inherited factors not every exposure will lead to cancer. The intensity and duration of exposure, combined with an individual's biological characteristics such as genetic makeup, and lifestyle factors determine each person's chances of developing cancer over his or her lifetime. In addition, when studying environmental cancer risk factors, it is important to consider that exposure to several environmental cancer risk factors may occur simultaneously. Growing knowledge of the environmental pollutants to which different segments of the U.S. population are exposed highlights new opportunities for education and policy initiatives to improve public health (13).

Outdoor air pollution is classified by the International Agency for Research on Cancer (IARC), an affiliate of WHO, as a potential cause of cancer in humans (244). Two types of air pollution are most common in the United States: ozone and particle pollution. Particle pollution refers to a mix of tiny solid and liquid particles that are in the air we breathe, and in 2013, IARC concluded that particle pollution may cause lung cancer. Nearly 21 million people in the United States were exposed year-round to unhealthy levels of particle pollution between 2018 and 2020 (83). Racial and ethnic minorities and people living in poverty were at an increased risk of being exposed to polluted air (83). New laws, regulations, and policies to reduce the release of pollutants into the atmosphere are urgently needed to reduce the adverse health effects of air pollution, including cancer.

Regulatory policies are also needed to combat the adverse health impact of wildfires considering the recent increase in these hazardous events in the Pacific Northwest. Wildfires emit many carcinogenic pollutants into the air, water, terrestrial, and indoor environments (245). There is emerging evidence that indicates long-term exposure to wildfires may increase the risk of certain cancers (245,246).

Individuals from **racial and ethnic minority** groups are **61 percent more likely** than White people to **live in a county with unhealthy levels of ozone and/or particle pollution** (83).

Certain chemical compounds that are used in agriculture, in the home, in some occupations such as pest control or weed control, and to protect us from fires, such as fire retardants, may cause cancer. The National Toxicology Program, a collaborative effort between the U.S. Department of Health and Human Services and IARC, has developed lists of substances that are known or are reasonably anticipated to be human carcinogens based on the available scientific evidence (242). Involuntary exposures to many of the environmental pollutants are usually higher in subgroups of the population, such as workers in certain industries who may be exposed to carcinogens on the job, racial and ethnic minorities, or individuals living in poverty (13). As we learn more about environmental and occupational cancer risk factors and identify those segments of the U.S. population who are exposed to these factors, new and equitable policies need to be developed and implemented for the benefit of all populations.

Screening for Early Detection

IN THIS SECTION YOU WILL LEARN:

- Breakthroughs in understanding of cancer initiation and progression are facilitating the development of cancer screening tests that can detect cancer at its earliest stage before it has spread to other sites.
- Authoritative professional organizations and government-affiliated agencies carefully evaluate the benefits and harms of cancer screening tests to make evidence-based recommendations for their use in the clinic.
- Technological advances, as highlighted by FDA approvals of software systems driven by artificial intelligence to aid cancer early detection and diagnosis, are poised to transform cancer screening in the coming years.
- There are substantial opportunities to save lives by developing evidence-based early detection of cancer types with high mortality rates, such as cancers of ovary, pancreas, and liver, for which there are currently no recommended screening tests available for the average-risk population.

In recent decades, researchers have made major progress in understanding the underlying causes of cancer development (see **Understanding How Cancer Develops**, p. 19). In parallel, technological innovations in DNA sequencing, cellular imaging, and collection and storage of biospecimens have enabled reliable and reproducible detection of the genetic, molecular, and cellular events that drive cancer initiation and progression. Collectively, these advances have accelerated the development of screening tests and examinations that can find precancerous lesions or cancers at the earliest stage of development when it is easier to treat them successfully.

Purpose of Routine Cancer Screening

Cancer screening is the evidence-based determination of whether a person has precancerous lesions or cancer before any signs or symptoms of the disease appear. While modifying certain behaviors can reduce the risk of developing cancer, routine screening for cancer can help find an aberration at the earliest possible time during cancer development. Health care providers use the information gleaned from a cancer screening test to make an informed decision on whether to monitor or treat, or surgically remove precancerous lesions or early-stage cancer before either progresses to a more advanced stage (see **Figure 6**, p. 47).

There are different kinds of cancer screening tests that include laboratory tests to determine the changes in cancer biomarkers in samples of tissues or fluids in the body and imaging procedures to look for abnormalities inside the body (see sidebar on **Ways to Screen for Cancer**, p. 48). In addition, clinicians may also determine whether an individual needs to be screened for certain types of cancer using visual examination to check for unusual features such as lumps or discolored skin and/or reviewing the medical and family histories to evaluate an individual's inherited, behavioral, and environmental risks of developing cancer.

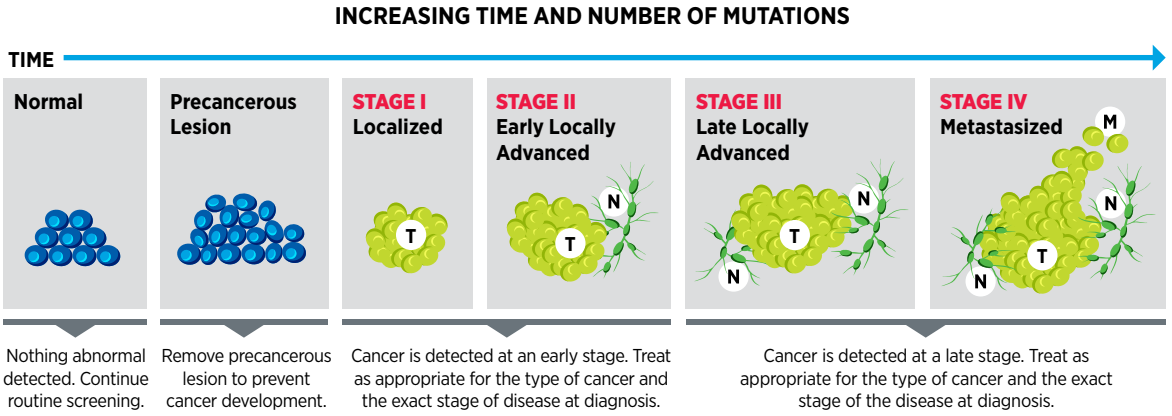
Detection of cancers through routine screening saves lives and improves quality of life by catching the disease early and treating it, and minimizing the risk of cancer progressing to an advanced, harder-to-treat stage (247). In 2020, findings from a landmark clinical trial evaluating the benefits of lung cancer screening showed a 25 percent decline in lung cancer deaths at a 10-year follow-up of more than 6,000 participants who underwent lung cancer screening from December 2003 to July 2006 (248). A recent study examined the impact of lung cancer screening guidelines issued in 2013 by the U.S. Preventive Services Task Force (USPSTF) and compared it with that of the 2021 revised guidelines. According to the study's findings, an estimated 6,845 and 23,444 additional lives would be saved from lung cancer if 30 percent and 100 percent of the population eligible under the revised guidelines were screened, respectively (249). Another recent study found that increasing the current levels of screening for breast, colorectal and cervical cancers to 100 percent will collectively save more than 45,000 lives (250). However, it is important to note that some screening tests are invasive medical procedures that can potentially cause harm (see sidebar on **Benefits and Potential Harms of Cancer Screening**, p. 49). Because of the potential harms, the risks and benefits of cancer screening are carefully considered for everyone.

Development of Cancer Screening Guidelines

The overarching goal of cancer screening is to reduce the burden of cancer in the general population. The key objective is to help individuals and their health care providers decide together whether an individual should be screened for cancer,

FIGURE 6

What Can Cancer Screening Find and What Can Be Done?



Cancers are progressive in nature. In the example depicted here, a normal cell contains an inherited genetic mutation or an acquired one. At this juncture in cancer progression, cancer screening tests are not able to detect the alterations even though the cell is predisposed to becoming cancerous. As the cell multiplies and acquires more genetic mutations, it gains precancerous characteristics (such as dysregulated cell proliferation and differentiation), and an increasingly abnormal precancerous lesion becomes detectable. Without any treatment, additional mutations accumulate over time, and the precancerous lesion evolves into a cancerous lesion (tumor; T) that spreads to nearby lymph nodes (N) and can ultimately metastasize (M) to other organs in the body. Solid tumors are usually staged using the TNM staging system. Because blood cells circulate throughout the body, cancers originating from different types of blood cells are staged differently from those that originate from solid tissues.

When a person is screened for a given cancer, several different things can be found depending on the stage at which cancer is diagnosed, and different outcomes can be predicted based on the finding. For example, the screening test may show that there is no abnormality present; if this is the case, the person should continue routine screening in close consultation with his or her provider to ensure that the benefits of routine cancer screening for the individual continue to outweigh any potential harms associated with cancer screening.

If the test detects a precancerous lesion, the lesion can be treated with preventive medication or risk-reducing surgery, thus minimizing the likelihood of its progression into cancer (see **Supplemental Table 1**, p 163). If the test finds a cancer at an early stage of development, for example, stage I or stage II for a solid tumor, the patient can be treated successfully with curative surgery or other type(s) of cancer treatment (e.g., radiation) and has a higher likelihood of survival. If the test detects cancer at an intermediate stage, there is still a chance of cure, albeit lower than if the cancer was detected at stage I or II.

Treatment of cancer with surgery, chemotherapy, radiotherapy, molecularly targeted therapy, and/or immunotherapy is less likely to be curative if the test detects cancer at a later stage of development, i.e., stage III or stage IV.

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

Adapted from (21).

at what age the screening should start and stop, and how frequently the screening should be done and by which method.

When developing cancer screening guidelines for the general population (i.e., those who are at an average risk of developing cancer), authoritative groups of subject matter experts consider age as well as several aspects that are specific to individuals or population groups for whom the screening guidelines are being developed. These considerations include whether or not a person has a particular organ (e.g., for cervical cancer screening, whether an individual never had a cervix or had a hysterectomy with cervix removal); has a smoking history

Ways to Screen for Cancer

Many cancer screening tests are medical procedures and can carry potential harms. The U.S. Preventive Services Task Force (USPSTF), which is an independent, volunteer panel of national experts in disease prevention and evidence-based medicine, reviews the accuracy and efficiency with which different tests can detect cancer, as well as any potential harms of those tests, as part of the process to develop evidence-based cancer screening guidelines.

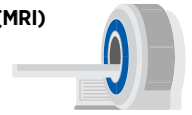
Described below are some cancer screening tests used in the clinic for the five most common cancer types for which there are evidence-based USPSTF screening guidelines for the general population (see sidebar on **USPSTF Guidelines for Screening Five Cancer Types**, p. 52). Not discussed are screening tests for cancer types for which there are no USPSTF-issued guidelines, such as the screening test for esophageal cancer that uses a capsule coated with a special protein and attached to a string for collection of cancer cells.

Unless indicated otherwise, many of the procedures listed here can detect cancer at any stage of development, but the aim of using them for screening purposes is to find the cancer at the earliest possible stage.

BREAST CANCER

Mammogram
Uses X-rays to generate two-dimensional images of the breast that can be stored on film (a conventional mammogram) or electronically (a digital mammogram) for further analysis. Some machines can generate three-dimensional images in a process called breast tomosynthesis.

Breast Magnetic Resonance Imaging (MRI)
Uses radio waves and a powerful magnet linked to a computer to create a detailed image of the breast.



Whole Breast Ultrasound
Uses ultrasonography to scan the entire breast, looking for lumps or nodules.

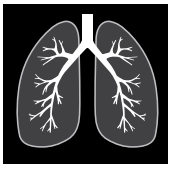
CERVICAL CANCER

Pap Test
Samples cervical cells, which are analyzed under a microscope to look for abnormalities.

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

LUNG CANCER

Low-dose Spiral CT Scan
Uses low doses of X-rays to rapidly image the lungs and detect any structural abnormalities suggestive of lung cancer. Suspicious lesions are then biopsied for diagnosis.

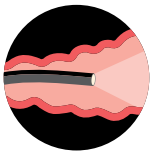


Adapted from (21).

COLORECTAL CANCER

Stool Tests
Some test for the presence of red blood cells in stool samples because colorectal cancer can cause rectal bleeding. Others test for both red blood cells and certain genetic mutations linked to colorectal cancer. These tests do not directly detect colorectal precancerous lesions or cancers but identify people for whom further testing is recommended.

Flexible Sigmoidoscopy and Colonoscopy
Use a thin, flexible, lighted tube with a small video camera on the end to allow physicians to look at the lining of the full length of the 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), and Double-contrast Barium Enema
Use X-rays to image the colon and rectum.

Blood Test
Detects genetic or epigenetic abnormalities linked to colorectal cancer in blood. This test does not directly detect colorectal precancerous lesions or cancers but identifies people for whom further testing is recommended.

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. This test does not directly detect prostate cancer but identifies men for whom further testing is recommended.

Benefits and Potential Harms of Cancer Screening

The U.S. Preventive Services Task Force (USPSTF) or authoritative professional societies focused on cancer care meticulously review the available scientific evidence to weigh potential risks of screening for a specific cancer type against benefits of screening for it before the cancer screening guidelines are issued for the general public. Benefits of USPSTF-recommended routine cancer screening are substantial and typically outweigh potential harms from the procedure, as described below. However, it is also important to note that benefits-to-potential harms ratio can vary for different population groups as well as for individuals at different points in their lives.

BENEFITS OF SCREENING

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

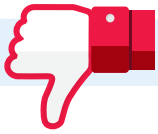
Reduced Likelihood of Advanced Disease
If a screening test detects cancer at an early stage of development, it can reduce an individual's risk of being diagnosed with the screened cancer at an advanced stage.

Reduced Cancer Mortality
If a screening test detects cancer at an early stage of development, it can increase the likelihood that a patient can be successfully treated.

Informed Behavioral Changes
If a screening test detects cancer, it can also indicate that making behavioral changes—for example eliminating exposure to cigarette smoke if a screening test finds early signs of lung cancer—will reduce the chances of developing another cancer caused by that behavior.

All these possibilities may increase quality of life and reduce an individual's risk of dying from the screened cancer.

POTENTIAL HARMS OF SCREENING



Adverse Events
Screening tests could carry minimal but measurable risks of side effects. For example, colonoscopy can potentially cause a puncture, cut, or tear in the wall of the colon.

Anxiety
Screening tests could cause unnecessary anxiety for individuals who do not have the disease.

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

False-negative Test Results
Screening tests could sporadically give negative results in individuals who are not free from the screened cancer, leading to missed opportunities for early treatment and/or behavioral changes.

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

(for lung cancer screening); has an all-negative prior screening history (for cervical cancer screening); has reduced life expectancy (for prostate cancer screening); has a family history (for colorectal and breast cancer screening); and/or belongs to a racial or ethnic minority group (for prostate cancer screening).

In the U.S., guidelines for cancer screening are meticulously developed by multiple authoritative groups and professional societies. For example, an independent group of experts convened by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services carefully evaluates data regarding the benefits and potential harms of different approaches to disease prevention, including cancer screening tests, genetic testing, and preventive therapeutics, to make evidence-based recommendations about the use of these in primary care settings. These volunteer experts form USPSTF (see sidebar on **How Are Cancer Screening Guidelines Developed?**, p. 50).

How Are Cancer Screening Guidelines Developed?

Authoritative panels of subject matter experts meticulously review the available evidence and carefully weigh benefits of cancer screening against any potential harms before recommending at what age a person should start or stop cancer screening, for which cancer type, how frequently, and by which method he or she should be screened. There are minor differences in the process used and the guidelines issued by different organizations, but the overall rigor that is put in place to ensure maximal benefit and minimal harms to public health and safety is similar.

THE USPSTF REVIEW PROCESS FOR DEVELOPING CANCER SCREENING GUIDELINES*

The U.S. Preventive Services Task Force (USPSTF) is convened by U.S. Department of Health and Human Services. During the development of cancer screening guidelines, USPSTF is supported by researchers from the Evidence-based Practice Center (EPC) program, a U.S. Agency for Healthcare Research and Quality initiative. Institutions in the United States and Canada are awarded five-year contracts to serve as EPCs.

Review Topic Nominations
Anyone can nominate a new topic for review at any time. USPSTF reviews, selects, and prioritizes nominated topics based on relevance to and impact on disease prevention, primary care, and public health.

Develop Draft Research Plan
USPSTF and EPC develop a research plan and seek expert input on the prioritized topic. USPSTF posts the draft research plan on its website for public comments.

Review Public Comments and Finalize Research Plan
USPSTF and EPC review public comments and revise research plan as needed. USPSTF posts the final research plan on its website.

Review Evidence and Develop Draft Recommendation
USPSTF assesses EPC-gathered evidence, weighing effectiveness and benefits/harms, and develops a draft recommendation statement, which is posted on the website, along with EPC evidence review, for public comments.

Review Public Comments and Finalize Recommendation
Both the draft recommendation and evidence review are revised and finalized based on public comments and published in peer-reviewed journals and on the USPSTF website.

THE USPSTF GRADING SYSTEM FOR CANCER SCREENING GUIDELINES†‡

For the finalized guidelines, USPSTF assigns a grade to its recommendations. It is important to note that, based on the available evidence, USPSTF can assign different grades to different subpopulations for screening for the same cancer type. For example, screening for colorectal cancer is a Grade A recommendation for adults ages 50 to 75 and a Grade B recommendation for adults ages 45 to 49. Below are simplified definitions of these grades:

Grade A: Screening recommended because of high certainty that net benefit is substantial.

Grade B: Screening recommended because of high certainty that net benefit is moderate.

Grade C: Selective screening recommended based on professional assessment and patient preferences because of moderate certainty that net benefit is small.

Grade D: Screening 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.

*In addition to developing screening guidelines for cancers, USPSTF issues guidance on a range of public health-related issues, such as cardiovascular disorders. The cancer-specific language usage here is only for the purpose of this report; the review process and grades described are applicable to all guidance issued by USPSTF.

†Definitions included here are based on grade definitions after July 2012. A complete description for each grade, and the definitions for the guidelines issued before July 2012, can be accessed at the USPSTF website (251).

‡Grade of evidence also informs which preventive services, including cancer screening, must be covered without out-of-pocket costs under the Affordable Care Act.

USPSTF recommendations for cancer screening tests fall into four categories, including recommendations for screening certain individuals at certain intervals (see sidebars on **USPSTF Guidelines for Screening Five Cancer Types**, p. 52, and **Differential Risks That Guide Cancer Screening Decisions**, p. 55), recommendations against screening, and deciding that there is insufficient evidence to make a recommendation. In addition to considering evidence regarding potential new screening programs, USPSTF reevaluates existing recommendations as new research becomes available and can revise the recommendations if necessary (see sidebar on **How Are Cancer Screening Guidelines Developed?**, p. 50). Occasionally, other professional societies focused on cancer care also issue screening guidelines.

Recent Advances in Cancer Screening and Early Detection

Characterization of molecular and cellular features that can help detect precancers or cancers at the earliest possible stage when it is easier to treat them successfully are areas of active research. In addition, researchers are working on developing novel strategies that can improve the efficacy, efficiency, and accuracy of cancer screening exams, while minimizing any potential harm from the procedure. Another area of ongoing research is to develop tools and tests that detect only those cancers that are most likely to progress to an advanced, aggressive stage.

HARNESSING THE POWER OF ARTIFICIAL INTELLIGENCE FOR EARLY DETECTION OF CANCERS

One area of intense research and rapid progress in recent years has been the use of artificial intelligence (AI) and machine learning to analyze large amounts of imaging data collected for the purposes of cancer screening and to recognize patterns that are otherwise time-consuming and difficult to discern by eye even by trained experts (see sidebar on **Artificial Intelligence in Early Detection**, p. 53). As one example, researchers developed an AI-enhanced model that used images from a person's mammograms to predict that person's likelihood of developing breast cancer in the next five years. The model's prediction was more accurate than currently available tools to assess a person's risk of developing breast cancer (252).

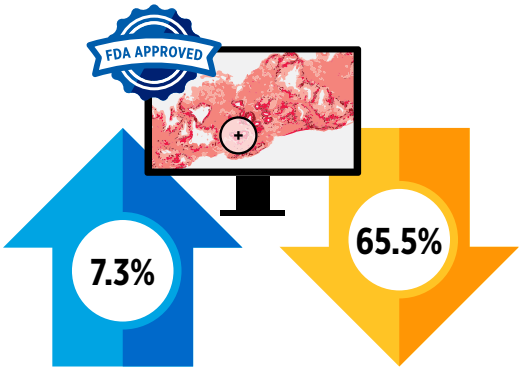
Although additional research is needed, some of the AI-driven medical devices and software have proven to be highly accurate and effective in clinical trials. From August 1, 2021, to July 31, 2022, the 12 months covered by this report, FDA approved many AI-enhanced software systems for assisting clinicians in detecting cancers early. Here, we are using examples of two such software systems—Lunit INSIGHT MMG and EndoScreener—to highlight the rapid advancement in this exciting area of cancer research.

In November 2021, FDA approved Lunit INSIGHT MMG, an AI-driven software that uses deep learning to analyze mammography images with high accuracy for detecting breast cancer (see sidebar on **Artificial Intelligence in Early Detection**, p. 53). Lunit INSIGHT MMG provides the location of lesions that could indicate breast cancer and assigns an abnormality score that reflects the software's confidence of the existence of lesions. The software was developed and validated using 170,230 mammography examinations, of which 36,468 were of breast cancer as confirmed by tissue biopsy. Researchers found that, compared to manual evaluation of mammograms by pathologists, the software was 12 percentage points more sensitive in detecting cancers with mass, and 40 percentage points more sensitive in detecting cancers that were asymmetrical or distorted in slide images (255). Another study compared the diagnostic accuracy and sensitivity of Lunit INSIGHT MMG with two commercially available AI-based software systems for the detection of breast cancer. Researchers subjected 8,805 mammograms, of which 739 had breast cancer diagnosis, to the analysis and found that Lunit INSIGHT MMG had 15 percent higher sensitivity compared to the other two algorithms (256).

In March 2022, FDA approved EndoScreener, an artificial intelligence software system that aims to identify potentially precancerous polyps during a colonoscopy. Polyps are clumps of usually benign cells that build up on the lining of the colon and can be precursors to colon cancer. The approval was based on findings of a clinical study reporting that EndoScreener detected about 32 percent more polyps than manual observation alone, decreasing the rates of missed polyps during colonoscopy to 20 percent from 31 percent using standard methods (257,258). Research has found that, during colonoscopy, about one third of precancerous lesions can go undetected, potentially delaying treatment for colorectal cancer (259). Approval of EndoScreener is expected

PAIGE PROSTATE

The first AI-based software approved by FDA to identify areas with suspected prostate cancer on the digitized images of prostate biopsy. A pathologist then reviews those detected areas of suspected cancer (254).



USPSTF Guidelines for Screening Five Cancer Types*

The U.S. Preventive Services Task Force (USPSTF) carefully reviews available data and weighs the risks and benefits for the broader population before issuing cancer screening guidelines (see sidebar on **How Are Cancer Screening Guidelines Developed?**, p. 50). As of July 31, 2022, USPSTF has guidelines for five types of cancer, four of which apply to individuals who are at an average risk of developing breast, colorectal, prostate, or cervical cancer. Guidelines for lung cancer apply to former or current smokers, individuals who are at a high risk of developing the disease because of tobacco use.

BREAST CANCER

Mammogram every other year for women ages 50 to 74. Women ages 40 to 49 should discuss with their health care provider to make an informed and shared decision on whether they should receive breast cancer screening. USPSTF last revised these guidelines in January 2016, and currently is in the process of updating them.†

See full recommendation here:
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening

CERVICAL CANCER

Cervical cytology every three years for women ages 21 to 65; high-risk human papillomavirus testing alone, or in combination with cytology, every five years for women ages 30 to 65. USPSTF last revised these guidelines in August 2018, and currently is in the process of updating them.

See full recommendation here:
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening

COLORECTAL CANCER

Stool-based tests every one to three years, and/or colonoscopy/flexible sigmoidoscopy every five to 10 years, for all adults ages 45 to 75. USPSTF last revised these guidelines in May 2021.

See full recommendation here:
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening

LUNG CANCER

Low-dose computed tomography (LDCT) every year for all adults ages 50 to 80 who are current smokers or who quit within the past 15 years, with a 20 pack-year smoking history. 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. USPSTF last revised these guidelines in March 2021.

See full recommendation here:
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening

PROSTATE CANCER

Periodic prostate-specific antigen-based test, after discussions with health care provider and through shared decision, for men ages 55 to 69. USPSTF last revised these guidelines in May 2018.

See full recommendation here:
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening

*Guidelines included here have been simplified for brevity. The USPSTF website contains additional important and most up-to-date information. Readers are encouraged to visit the provided USPSTF webpages for each of the guidelines

†Only USPSTF guidelines are included in this sidebar. Several other professional societies issue evidence-based screening guidelines for certain types of cancer that may differ from those issued by USPSTF. For example, certain organizations recommend that women should undergo screening mammography beginning at age 40 years.

Artificial Intelligence in Early Detection

ARTIFICIAL INTELLIGENCE (AI)

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

MACHINE LEARNING (ML)

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

DEEP LEARNING (DL)

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

BENEFITS OF AI IN CANCER DETECTION

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

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

BARRIERS IN THE USE OF AI IN CANCER DETECTION

- The **lack of large, well-annotated cancer datasets** that are representative of the diverse patient population as well as of the distinct cancer burdens of various population groups is a significant barrier for the use of AI in cancer research and patient care.
- The use of AI in early detection and diagnosis of cancer is **still in its infancy**; all stakeholders must work together to ensure an equitable uptake of this major technological advance in cancer science and medicine.
- Because the use of AI in medicine is a newer technological advance, there may be **concerns among patients about the use of their medical records**, including images and tissues.

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

APRIL 2021

GI Genius
A medical device that uses AI-based software to assist clinicians in identifying precancerous lesions or polyps that may not be detectable otherwise during routine colonoscopy (21).

SEPTEMBER 2021

Paige Prostate
An AI-based software that reviews digitally scanned slide images from prostate biopsies to assist pathologists in the detection of areas that are suspicious for cancer.

NOVEMBER 2021

Lunit INSIGHT MMG
An AI-based software that analyzes mammography images and provides the location of breast lesions suspected of being cancerous (see text for more detail).

MARCH 2022

EndoScreener
An AI software system that aims to identify potentially precancerous polyps during a colonoscopy (see text for more detail).

Developed from (253).

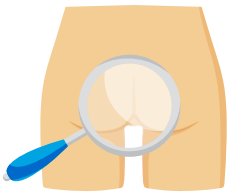
to substantially improve detection of precancerous lesions during colonoscopy (259).

Selected approvals discussed here underscore the rapid advances in routine use of AI in the clinic for early detection and diagnostic purposes. Use of AI in other aspects of cancer research and patient care—genomic characterization of tumors; drug discovery; and improved cancer surveillance—is an active area of investigation (see **Artificial Intelligence**, p. 120) (260).

MAPPING A COURSE FOR CANCER DETECTION AT THE EARLIEST POSSIBLE STAGE

It can take decades for normal cells to turn cancerous from the first genetic and/or epigenetic alterations. During this time, cells can remain in a precancerous state, sometimes evading detection by the immune system and on their way to becoming malignant.

Treating anal precancerous lesions in people living with HIV **reduces the chance of developing anal cancer** by more than half (262).



One of the ongoing initiatives to characterize the precancerous state is the Human Tumor Atlas Network (HTAN). Launched in September 2018, HTAN is an NCI-funded Cancer Moonshot initiative through which a collaborative network of Research Centers and a central Data Coordinating Center is working to identify the molecular and cellular events that cause healthy cells to become precancerous and cancerous. Some of the cancers for which HTAN is developing the so-called "precancerous atlases" include cancers of the lung, pancreas and breast (261).

In-depth knowledge of the precancerous state can offer an opportunity not only to detect cancer at the earliest possible stage, but also to intervene before a cell becomes cancerous, a concept called cancer interception.

MOVING TOWARD MINIMALLY INVASIVE CANCER TESTING

Some of the tests used for cancer screening are invasive medical procedures, with potential health risks. Furthermore, most cancer screening tests are designed to detect only one type of cancer. Research has revealed that precancerous lesions and tumors shed a variety of cellular material, such as cells, microscopic lipid vesicles called exosomes, and/or cell-free DNA, RNA, or proteins. Any of these materials can be detected in blood or other body fluids, such as urine, using a minimally invasive procedure called liquid biopsy. Liquid biopsy approaches are in routine use for analyzing tumor-associated genetic alterations using circulating tumor DNA, and for making treatment decisions and/or monitoring for signs of cancer's return in those individuals who have already received cancer treatment. Researchers are developing early detection tests that are minimally invasive and can screen for many cancer types simultaneously, thus making it easier for individuals being screened. These tests will also likely decrease potential harm(s) from conventional cancer screening tests to individuals being screened.

As one example, in a recent study of 2,094 patients, researchers combined liquid biopsy to detect multiple cancers using a small amount of a patient's serum with machine learning to differentiate cancer from noncancer samples. Findings of the study reported that the test was able to accurately detect eight types of cancer at various stages of development with nearly 90 percent sensitivity and 61 percent specificity (263). This and other similar studies underscore the immense promise of multicancer early detection tests, but additional research is needed before they can be routinely used in the clinic.

A minimally invasive test that can be used to screen for multiple cancer types reliably can revolutionize early detection of cancers by minimizing harm for the individual being screened; by potentially increasing adherence to routine cancer screening; and by potentially decreasing the financial and logistic barriers to cancer screening.

Factors That Determine Whether Individuals Should Receive Cancer Screening

A person's risk of developing cancer is determined by many factors including inherited, environmental, and lifestyle influences, some of which may change throughout life. Thus, the decision of whether someone should be screened for cancer, at what age, and for which cancer type(s) is different for each person and may change over the course of their lives (see sidebar on **Differential Risks That Guide Cancer Screening Decisions**, p. 55). It is important that people consult with their health care providers to develop a personalized cancer screening plan that considers their risk of developing a cancer and their tolerance for the potential harms of a screening test.

Suboptimal Adherence to Cancer Screening Guidelines

Suboptimal adherence to cancer screening guidelines means when an eligible individual is not up to date with routine cancer screening as recommended by USPSTF guidelines, or when an individual for whom the routine cancer screening is no longer recommended continues to receive it. Despite the many benefits of routine cancer screening, underscreening—the underuse of routine cancer screening among eligible individuals—is common. As one example, only 67 percent of adults who were eligible for routine colorectal cancer screening in 2018 were up to date with routine screening (264). One recent study estimated that increasing the use of screening for colorectal cancer alone from 67.7 percent (levels of colorectal cancer screening in 2016, the data year of the study) to 100 percent could have prevented an additional 35,530 deaths over the lifetime of an adult age 50 (250), underscoring the importance of cancer screening in early detection and its potential in saving lives.

While being up to date with routine cancer screening guidelines is key to early detection, it is also important to know when an individual should stop screening for cancer. USPSTF guidelines include the age past which the potential harms from screening tests are likely to outweigh a net benefit (see sidebar on **USPSTF Guidelines for Screening Five Cancer Types**, p. 52). However, overscreening, e.g., the use of screening tests beyond the recommended age, is common. As one example, researchers found that at least half of older U.S. adults in 2018 had received at least one unnecessary screening test for breast, cervical, or colorectal cancer in the past few

Differential Risks That Guide Cancer Screening Decisions

Cancer screening refers to checking for precancerous lesions or cancer in people who have no signs or symptoms of the cancer for which they are being tested. The decisions of whether someone should be screened for cancer, at what age the screening should begin, for which cancer type(s) the individual should be screened, and at what age the routine screening should stop, are different for each person. Broadly speaking, individuals fall into two categories for cancer screening:

INDIVIDUALS AT AVERAGE RISK OF DEVELOPING CANCER

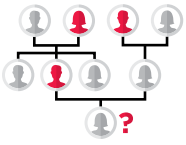
In general, individuals at average risk of developing cancers are those who do not have a strong family history of cancer or personal history of cancer, and do not have an inherited genetic condition or lifestyle factor that places them at high risk of developing cancer.

INDIVIDUALS AT HIGH RISK OF DEVELOPING CANCER

There are also other factors that may help determine whether an individual should consider undergoing cancer screening. Some of these factors, which may put an individual at a higher risk for developing cancer, are described below:

Individuals with increased exposure to one or more cancer risk factors:
For example, individuals who smoke tobacco are at a higher risk for developing cancer. According to CDC, people who smoke cigarettes are 15 to 30 times more likely to develop lung cancer or die from it than people who do not smoke.

Individuals with a unique cellular or tissue makeup:
For example, women who have extremely dense breasts have an increased risk of developing breast cancer compared to women with less dense breasts. As another example, women who have certain patterns of "overactive" breast tissue in an otherwise benign breast biopsy (e.g., atypical cells or lobular carcinoma in situ) are also at increased risk for developing breast cancer.



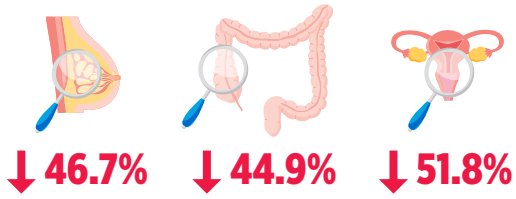
Individuals with inherited cancer susceptibility syndromes:
Also called hereditary cancer syndromes, inherited cancer susceptibility syndromes are caused by genetic mutations that can be passed on from one generation to the next and can predispose an individual to develop certain types of cancer. For example, individuals who have certain mutations in the BRCA1/2 genes or have a strong family history of breast cancer are at a higher risk of developing cancers of breast, ovarian and pancreas.

Individuals who consider themselves at a high risk for inheriting a cancer-predisposing genetic mutation should consult a health care provider and consider genetic testing and genetic counseling. Genetic testing may aid an individual and his or her health care provider team in deciding whether a preventive surgery would help reduce the risk of developing cancer later on (see **Supplemental Table 1**, p. 163)

Individuals from certain racial and ethnic minorities:
Those who belong to certain racial and ethnic minorities are at a higher risk of developing certain types of cancer and at a younger age compared to White individuals. For example, accruing evidence shows that a breast cancer diagnosis at a younger age is more common in Black women compared to White women. Furthermore, Black women are more likely to be diagnosed with biologically aggressive forms of the disease at all ages.

Adapted from (13).

Globally, routine screening decreased 46.7 percent for breast cancer, 44.9 percent for colorectal cancer, and 51.8 percent for cervical cancer **during January-October 2020** compared to the same timeframe from the previous year (272).



years (265). There is also evidence that continuing cancer screening beyond the recommended age may be beneficial for some older adults (266). It is of utmost importance that older adults make an informed and shared decision with their provider whether to continue screening for cancer that is tailored to their health status and life expectancy, as well as to their specific exposure to genetic, environmental, and modifiable risk factors (267-269).

As highlighted in the *AACR Cancer Disparities Progress Report 2022*, released in June 2022, cancer screening rates are substantially lower among those from racial and ethnic minorities and other medically underserved populations (13). Furthermore, screening patterns vary for different types of cancer and/or screening tests (270). Barriers such as access to health insurance, low health literacy, and miscommunication between patients and providers contribute to low screening rates (271).

As detailed in the *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care*, released in February 2022, severe interruptions in routine cancer screening, especially during the initial months of the pandemic, may have exacerbated the existing disparities in cancer screening (8). Screening rates for all five cancers declined significantly during the peaks of COVID-19, although more recent data indicate that screening rates for some cancer types are returning to prepandemic levels. Furthermore, professional organizations are teaming up to help increase the uptake of cancer screening that has been impacted by the pandemic (see sidebar on **COVID-19 Pandemic and Cancer Screening**, p. 56).

Here, we focus our discussion on the disparities in screening for five cancer types for which USPSTF currently has population-based screening guidelines and discuss some of the interventions that have helped close the disparity gap in cancer screening.

Unfortunately, not all segments of the U.S. population benefit equitably from routine cancer screening (see sidebar on **Disparities in Adherence to Cancer Screening Guidelines**, p. 60). The reasons for disparities in cancer screening are multifactorial and include lack of access to health care;

COVID-19 Pandemic and Cancer Screening

COVID-19 IMPACT ON CANCER SCREENING

9.4 million missed screenings for breast, colorectal, and prostate cancers in 2020 in the U.S. (273).

THE RETURN-TO-SCREENING PROGRAM

A collaborative effort between public health-focused professional organizations to increase the uptake of cancer screening (274):

Participants:

748 cancer facilities across the U.S.

Timeframe:

June through November 2021

Purpose:

Increase the rate of up-to-date breast, cervical, colorectal, and lung cancer screening

Percentage of facilities with monthly screening deficits:

- Breast cancer – 55.3 percent
- Cervical cancer – 69 percent
- Colorectal cancer – 80.6 percent
- Lung cancer – 44.6 percent

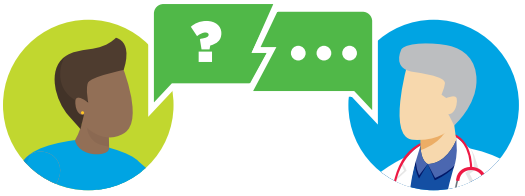
Strategies to raise awareness of cancer screening:

- Social media campaigns
- Patient and provider education

Goal:

70,000 additional cancer screenings per month by the end of the 6-month period.

In February 2022, the President's Cancer Panel released the report, ***Closing Gaps in Cancer Screening: Connecting People, Communities, and Systems to Improve Equity and Access***. The report, presented to President Biden, **outlined barriers and provided recommendations to improve cancer screening and follow-up care** in the United States.



Findings from a **recent survey of the members of sexual and gender minority (SGM) communities highlight gaps in patient-provider communications about cancer screening**:

- **Almost half** (48 percent) of SGM patients over age 45 surveyed **said their doctors never brought up cancer screenings**.
- A 54 percent **majority did not feel confident** "at all" about what, if any, cancer **screenings they needed to schedule** (283).

reduced rate of follow-up if the initial screening test indicates that cancer may be present; fear of cost; lack of health literacy about the benefits and potential harms of cancer screening; distrust in the health care system; and/or miscommunications between patient and provider (13).

Another research area in cancer screening that requires immediate attention from all stakeholders is the disparities in routine cancer screening among SGM populations, especially among transgender individuals. A recent study reported that, compared to cisgender individuals, only 32 percent of individuals transitioning from female to male had undergone breast cancer screening; these individuals were also 58 percent less likely to adhere to cervical cancer screening (282). These findings highlight the urgent need to develop cancer screening guidelines that are specific to members of the SGM community and to implement culturally and socially sensitive interventions that help improve health care experiences of the SGM community in the U.S.

Progress Toward Increasing Adherence to Cancer Screening Guidelines

Eliminating inequities in cancer screening and increasing the uptake of routine cancer screening among eligible individuals require multilevel and multipronged approaches to achieve equitable access and optimal adherence to cancer screening. These approaches include dismantling structural racism, discrimination, and other societal inequities that pose significant barriers in access to cancer screening; raising the awareness of cancer screening among eligible individuals, especially those belonging to racial and ethnic minorities and other medically underserved populations; effectively communicating benefits and potential harms of cancer screening; developing culturally tailored interventions that address the lack of health literacy and cancer screening knowledge among certain populations; making cancer screening accessible and convenient to all—both in availability and cost; and conveying the importance of follow-up visits if the initial screening exam indicates the possibility of cancer. Stakeholders across the cancer care continuum—cancer researchers, physicians, federal regulatory and funding agencies; cancer-focused professional organizations; patient advocates and navigators—are working together to achieve this goal, and many established as well as innovative interventions are being tested across the nation (see sidebar on **Approaches to Increase Adherence to Cancer Screening**, p. 61).

Although approaches discussed in this chapter are raising awareness of the importance of routine cancer screening among eligible individuals, concerted and coordinated efforts by stakeholders across the cancer care continuum are needed to maximize the impact of these strategies in achieving equitable public health. Professional organizations, government agencies, and policy makers focused on public health are advocating for a comprehensive national strategy to increase adherence to screening guidelines (289). A key component of such strategies is legislation for easy access to cancer screening as discussed by **Congressman Brian Fitzpatrick** (see p. 58).

At the federal level, NCI and CDC play important roles in raising awareness for cancer screening. For example, the Colorectal Cancer Control Program (CRCCP) of CDC seeks to increase screening through implementation of some or all four of the CDC-prioritized, evidence-based interventions (patient reminders, provider reminders, reducing structural barriers, provider assessment and feedback) and four optional supporting activities (small media, e.g., videos and brochures, professional development and provider education, patient navigation, and community health workers) (290). To achieve this goal, CDC partners with clinics, hospitals, and other health

Continued on page 60

The Honorable Brian Fitzpatrick

Your brother, former Congressman Mike Fitzpatrick, was featured in the *AACR Cancer Progress Report 2013*, in which he shared his moving story of surviving colon cancer. He tragically lost his subsequent battle against melanoma. Could you share how your brother's battles against cancer, and those of others close to you, have influenced your work in Congress?

My brother, Mike, was my role model. He served in Congress before me and taught me a lot about being a brother, friend, and how to best serve the people of Pennsylvania. His courageous battle with cancer showed me his values of perseverance in the face of overwhelming odds. I want to do right by him and help those around me in any way I can. I will continue to serve and will work towards helping find solutions to better cancer screening, research, and treatment.

How has that personal experience shaped your approach to health policy and the importance of funding for cancer screening, prevention, and research?

Cancer is the second-leading cause of death in the United States. It is a disease that affects so many people and their families, including myself. I also have dedicated a lot of my efforts to raising awareness for pediatric cancer research. That is why I introduced the bipartisan Fairness to Kids with Cancer Act, which takes steps to ensure pediatric cancer researchers have the funding necessary to save the many lives of children fighting cancer. There are few things more heart-wrenching than seeing a child battle cancer. No child should ever have to suffer through the pain of cancer, nor should any parent have to watch their child struggle and fight to survive. If I'm able to play even a small role in helping citizens in our country be better protected against cancer, I am going to do it.

Which policy priorities or legislative efforts do you share that would fuel better prevention, detection, and treatment of cancer?

I have made it my mission to sign on to legislation that will help advance cancer prevention, detection, and treatment. It is important that all Americans, regardless of their wealth and where they live, have access to cancer screening. I recently introduced the Screening for Communities to Receive Early and Equitable Needed Services (SCREENS) for Cancer Act, which would make screening services for breast and cervical cancer more widely available to women in America. Early testing for cancer saves lives and the SCREENS for Cancer Act is a step in the right direction at putting an end to cancer deaths. I have also made cancer research funding a top priority throughout my time in Congress. That is why this Congress I introduced the KO Cancer Act, which aims to provide a once-in-a-generation massive investment in cancer research funding, increasing cancer research funding allocated to the National Institutes of Health (NIH) by 25 percent, to reflect that cancer is the second leading cause of death in the U.S. Current federal funding levels for cancer research do not match the rate at which people are suffering and dying from this lethal disease. Legislation like this is for all of the victims, survivors, families, and friends whose lives have been impacted by cancer. As is the case for so many in America, this fight is personal to me. We must not stop until we eradicate this disease forever and spare parents, children, and families the pains of cancer.

What is your message to the scientists and physicians working to make progress against cancer?

Thank you for what you're doing to advance medicine and treatment for those suffering from cancer and other long-term illnesses. Your efforts are valued and appreciated, regardless of the results they produce. These studies introduce new ideas, knowledge, and perspectives on ways to treat cancer patients and I look forward to the day when we find the answer we've been searching for and can put an end to cancer deaths across the world.

"As is the case for so many in America, this fight is personal to me. We must not stop until we eradicate this disease forever and spare parents, children, and families the pains of cancer."

U.S. REPRESENTATIVE • PENNSYLVANIA'S 1ST DISTRICT

Disparities in Adherence to Cancer Screening Guidelines

Racial and ethnic minorities and other medically underserved populations experience disparities in adhering to cancer screening, as well as in following up with their health care provider if the initial cancer screening test indicates a possibility of cancer. Examples presented here highlight cancer screening disparities as evidenced in recent studies:

14% less likely	**AMERICAN INDIAN OR ALASKA NATIVE (AI/AN) INDIVIDUALS** AI/AN women were **14 percent less likely to be up to date with cervical cancer screening** compared to White women (264).
12% less likely	**ASIAN INDIVIDUALS** New York City residents from South Asia were **12 percent less likely to be up to date with colonoscopy** compared to the White residents of New York City (275).
53% less likely	**BLACK INDIVIDUALS** Non-Hispanic Black individuals eligible for lung cancer screening with low-dose computed tomography (LDCT) were **53 percent less likely to have completed LDCT** within the past one year compared to eligible non-Hispanic White individuals (276).
24% less likely	**HISPANIC INDIVIDUALS** Hispanic/Latino individuals were **24 percent less likely to be up to date with colorectal cancer screening** compared to non-Hispanic White individuals (277).
66% less likely	**NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER (NHOPI) INDIVIDUALS** NHOPI women were **66 percent less likely to screen for cervical cancer with Pap test** compared to White women (278).
19% less likely	**RURAL RESIDENTS** Women residing in rural areas were **19 percent less likely to undergo colorectal cancer screening** compared to those residing in urban areas (279).
46% less likely	**SEXUAL AND GENDER MINORITIES** Individuals who were born with a cervix and self-reported as belonging to a sexual minority were **46 percent less likely to undergo cervical cancer screening** compared to heterosexual individuals (280).
13% less likely	**LOW-INCOME INDIVIDUALS** Women with an annual household income of $25,000 or less were **13 percent less likely to undergo breast cancer screening** compared to those with an annual household income of $50,000 or more (281).

care organizations to use and strengthen strategies that have been shown to increase screening. A recent evaluation of 355 clinics that partnered with CRCCP across the country showed that >90 percent of the clinics implemented and fully integrated into their health systems at least two of the four evidence-based strategies by the third year of the partnership (291). Initial findings from the program indicate that the longer the clinics participate in the program the greater the increase from

Approaches to Increase Adherence to Cancer Screening

Multifactorial reasons lead to disparities in adherence to routine cancer screening, and thus require multipronged approaches to increase the uptake of cancer screening among eligible individuals. Below are examples of some of the strategies that have proven not only to increase cancer screening adherence among eligible individuals but also to decrease or, in some cases, even eliminate mortality from the cancer type for which the screening approach was developed:

COMPREHENSIVE PUBLIC HEALTH CAMPAIGNS

The Citywide Colon Cancer Control Coalition, a comprehensive public health campaign in New York City, **increased the number of those receiving timely colonoscopy** from 35 percent in 2003 to 72 percent in 2016 for Black residents and from 48 percent in 2003 to 67 percent in 2016 for White residents (284).

ACCESS TO HEALTH INSURANCE

Between 2017 and 2019, **lung cancer screening increased** by 16.2 percentage points among men who became eligible for Medicare at the age of 65 compared to men who were slightly younger than age 65 and were not eligible for Medicare (285).

CULTURALLY TAILORED INTERVENTIONS AND COMMUNITY ENGAGEMENT

De Casa en Casa, a culturally tailored approach to increase the uptake of cervical cancer screening among Hispanic women along the U.S.-Mexico border, **increased the likelihood of getting screened by 14 times** among those who received the intervention compared to those who did not (286).

REDUCTION OF STRUCTURAL BARRIERS

A campaign that eliminated the need for eligible individuals to visit a clinic for routine colorectal cancer screening **increased the completion of screening by nearly 10-fold**. Intervention participants received a series of reminder texts and a free fecal immunochemical test to use at home compared to those in the control group who only received a single text message reminding them that they were overdue for colorectal cancer screening (287).

IMPROVED PATIENT-PROVIDER COMMUNICATION

Use of email between patients and providers for communication about the importance of breast, cervical, and colorectal cancer screening **increased the likelihood of getting screened** for breast cancer by 32 percent, cervical cancer by 11 percent, and colorectal cancer by 55 percent compared to those who did not use email for communication (288).

baseline in their CRC screening rates. For example, screening rates increased, on average, by 8.2 percentage points and 12.3 percentage points for clinics that participated in the program for two years and four years, respectively (290).

The impact of these interventions on increasing colorectal cancer screening among eligible individuals is expected to become even more pronounced in the coming years.

Decoding Cancer Complexity. Integrating Science. Transforming Patient Outcomes.

IN THIS SECTION YOU WILL LEARN:

- Researchers are harnessing the knowledge gleaned from the molecular underpinnings of cancer initiation and progression to develop safer and more effective treatments.
- Advances in novel and innovative approaches to surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—the five pillars of cancer treatment—are saving and improving lives.
- From August 1, 2021, to July 31, 2022, FDA has approved eight new anticancer therapeutics and two new imaging agents, and has expanded the use of 10 previously approved anticancer therapeutics to treat additional cancer types.
- Included in the FDA approvals are a first combination of a radiodiagnostic agent to visualize cancer and a radiotherapeutic agent to kill cancer; several new and improved molecularly targeted therapeutics to treat rare cancers and cancers of the blood system; a new immune checkpoint inhibitor against a novel target; and a new immunotherapeutic to treat a rare and deadly form of eye cancer for which there was no standard treatment available.
- 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.

Recent decades have seen tremendous progress against cancer, as evidenced by a 26 percent decline in cancer-related deaths in the U.S. between 2000 and 2019, the most recent data year (5) (see **Cancer in 2022**, p. 8). The rapid pace of progress against cancer is in part driven by the availability of new and effective ways to treat cancers. Furthermore, advances in other aspects of cancer care have significantly improved the quality of life for cancer survivors (see **Supporting Cancer Patients and Survivors**, p. 102). Breakthroughs in cancer science and medicine are catalyzed by years-long cross disciplinary collaborations among stakeholders working throughout the medical research cycle (see **Figure 7**, p. 63).

Medical Research

Medical research is a continuous process with the goal to refine and improve clinical care and overall health for all individuals (see **Figure 7**, p. 63). During this process, researchers address the hypothesis of whether a new discovery or an observation—made at any step of the medical research cycle—has any biological and/or clinical significance. This is achieved through experiments in a wide range of models that mimic healthy and diseased conditions. Findings from these experiments can identify new targets for drug development; inform approaches for preventive intervention; determine new strategies for early detection; or uncover predictive or prognostic biomarkers, each of which has the potential to improve public health. Once a potential therapeutic target is identified, several candidate therapeutics against the target are carefully tested to determine the appropriate dosage, dosing schedules, and potential toxicities (see sidebar on **Therapeutic Development**, p. 64). These preclinical studies help determine the most promising candidates, which are then tested in clinical trials.

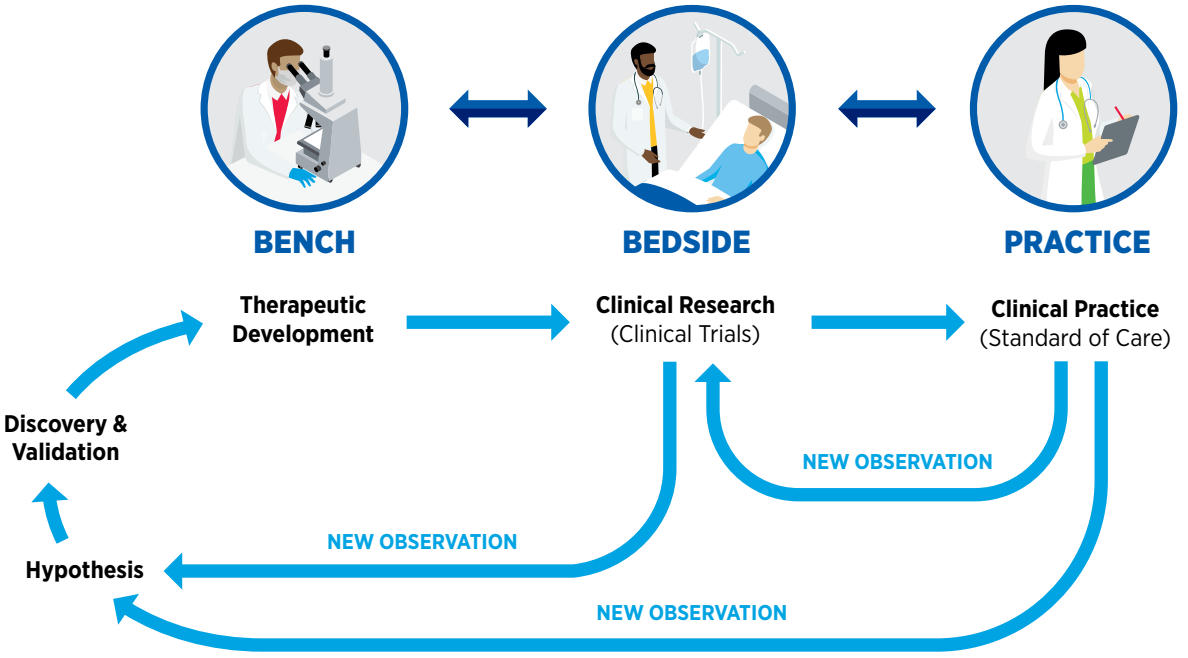
CLINICAL STUDIES

Once FDA approves a clinical candidate for testing in humans (see sidebar on **Therapeutic Development**, p. 64), researchers conduct studies to evaluate safety and efficacy of the clinical candidate in humans. These clinical studies are an integral part of medical research and, together with basic research, make up the backbone of cancer science and medicine. Evidence gathered from clinical studies is reviewed by FDA to determine whether a therapeutic should be approved for use in the clinic.

There are various types of clinical studies, each developed to address specific research questions—although many can also provide answers to additional research questions (292) (see sidebar on **Types of Clinical Studies**, p. 65).

FIGURE 7

The Medical Research Cycle



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

In addition to fueling the development of safer and more effective therapeutics, scientific knowledge gathered through the medical research cycle informs evidence-based guidelines for cancer screening and treatments as well as public health policies and regulations.

Adapted from (21).

Clinical studies, also called clinical trials, are carefully designed by clinicians and researchers involved in the study, and the conduct of clinical trials is meticulously reviewed and approved by institutional review boards. Clinical studies in which participants are randomly assigned to receive experimental treatment or standard of care treatment are called randomized clinical trials and are considered the most rigorous. Although an inactive agent, also called placebo, is rarely used in cancer clinical trials, researchers sometimes include it in the clinical trial design when there is no standard of care treatment available.

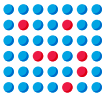
The design of randomized clinical trials prevents biases and increases the accuracy of the outcomes (293). The rigor in design and conduct of clinical trials is essential because these studies involve the use of experimental therapeutics and aim to extrapolate conclusions for the entire population based on data from a group of participants. For this reason, clinical trials are also closely monitored throughout the duration of the study to ensure safety of the participants.

The design of a treatment clinical trial depends on the type of anticancer agent and whether it is being tested alone or in combination with other anticancer treatments; the type of cancer; size and demographics of the clinical trial participants; and the infrastructure in place to support successful completion of the clinical trial, among other considerations. Furthermore, rapidly

Therapeutic Development

TARGET VALIDATION

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

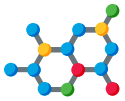


DRUG SCREENING

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

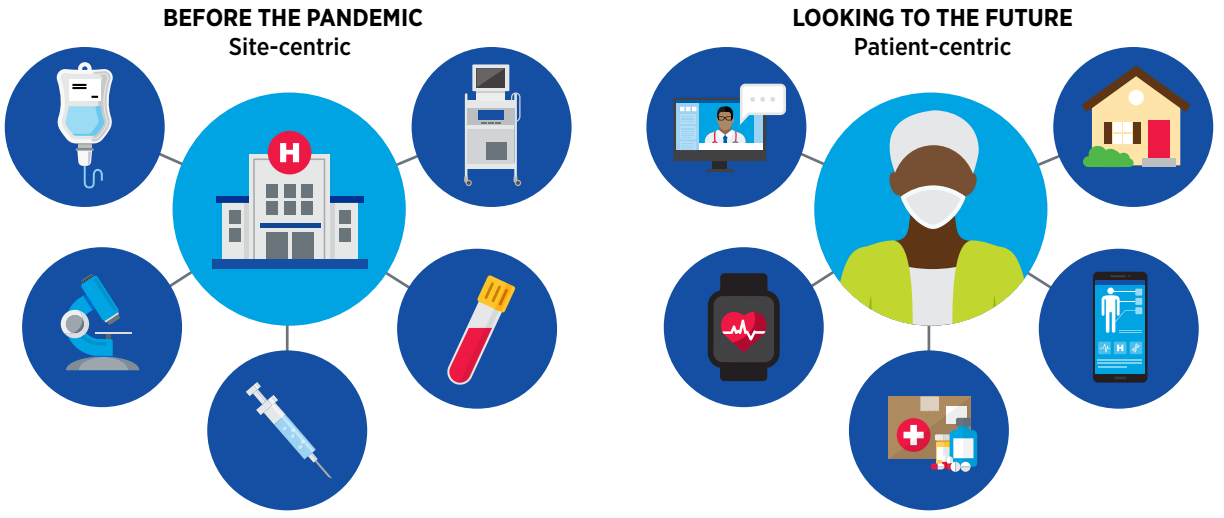
Optimized lead compound(s) are tested in cell-based and animal models for effectiveness, potential toxicity, optimal starting dose, and dosing schedule for clinical or "first-in-human" testing. The final compound(s) are considered the clinical candidate(s).

INVESTIGATIONAL NEW DRUG

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

Adapted from (21).

CANCER CLINICAL TRIALS

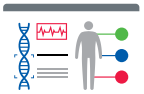


Types of Clinical Studies

Each clinical study (also called clinical trial) is designed to address specific research questions. Furthermore, many clinical trials can also provide answers to additional 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. In oncology, there are multiple types of clinical trials:

PREVENTION TRIALS

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



SCREENING TRIALS

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

DIAGNOSTIC TRIALS

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

TREATMENT TRIALS

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

QUALITY OF LIFE TRIALS

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

NATURAL HISTORY OR OBSERVATIONAL STUDIES

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

CORRELATIVE STUDIES

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

evolving understanding of the molecular underpinnings of cancer development means that there is a marked increase in the number of drugs that act against specific molecular targets. This knowledge has spurred the growth of precision medicine and has necessitated changes to the design and conduct of clinical trials (see sidebar on **Conduct of Clinical Trials**, p. 66). Furthermore, clinical studies can take years to complete. In recent years, FDA—the federal agency that oversees clinical trials and drug approvals—has made important procedural changes to expedite the conduct and review of clinical trials (see **Diversifying and Decentralizing Clinical Trials**, p. 131).

Despite improvements in both the clinical trial design and drug approval regulatory processes, there are other opportunities to further minimize the time it takes for a lifesaving anticancer therapeutic to reach patients who will benefit from it the most. The COVID-19 pandemic, despite its adverse effects on nearly all aspects of cancer science and medicine (8), including on clinical trials, has offered a blueprint of success to further revise and reform clinical trials and the drug approval process for the benefit of cancer patients.

Researchers are hopeful that the modifications to clinical trials as a result of the knowledge gleaned from the COVID-19 pandemic may also address the serious lack of representation from racial and ethnic minorities and other underserved populations which remains the most pressing challenge in clinical research. Recruitment of clinical trial participants

Conduct of Clinical Trials

Clinical trials are pivotal to making progress against cancer. There are many ways researchers can design a clinical trial.

A clinical trial can be **nonrandomized**, which means that participants are not assigned by chance to different treatment groups, and may choose which group they want to be in, or they may be assigned to the groups by the researchers.

A clinical trial can be **randomized**, which means that participants are divided by chance into separate groups that compare different treatments or other interventions.

Highlighted below are major designs of traditional and modern clinical trials:

TRADITIONAL CLINICAL TRIALS

Conducted in successive phases to test an investigational anticancer therapeutic in humans. Traditional clinical trials remain an integral part of clinical research:

Phase I

Studies involve tens of patients and determine safety and dosage.*

Phase III

Studies involve thousands of patients and determine efficacy of the new drug in comparison to standard of care.†

Phase II

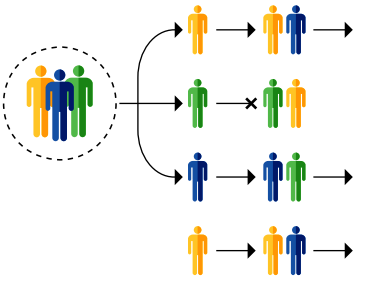
Studies involve hundreds of patients and determine safety and initial efficacy.*

Phase IV

Studies are conducted after a therapy is provisionally approved by FDA and provide additional effectiveness or "real-world" data on the therapy.

MODERN CLINICAL TRIALS

Conducted as parallel substudies or experimental arms and driven by genomics to test multiple drugs against the same cancer type or a single drug against multiple cancer types. Parallel experimental arms within modern clinical trials typically include different phases of conventional clinical trial design, and are typically randomized:



Adaptive Design

Allows for making prespecified planned changes to one or more aspects of the study based on accumulating data from participants in the trial. Because of the complexity of the design, adaptive clinical trials may require a large number of participants and a well-established clinical infrastructure to support the study.

Main Protocol (Also called Master Protocol)

Answers multiple questions within a single overall clinical trial. Following are examples of clinical trials that use the main protocol:

- **Basket trials** test one drug against multiple cancer types that have the same genetic characteristic. This trial design requires fewer participants before safety and efficacy of the drug are determined, and/or decreases the time it takes for the drug to be tested and made available to patients.
- **Umbrella trials**‡ test multiple drugs against a single cancer type. This trial design allows participants to be assigned to different treatment arms based on the molecular characteristics of their cancer.
- **Platform trials**‡ provide an infrastructure for evaluating multiple targeted therapies for one or more cancer types through ongoing changes in experimental arms. They are typically randomized. These trials contain a control arm and multiple experimental arms that undergo adaptive changes based on accumulating data from participants in the trial. A shared control arm allows researchers to assign more participants in the experimental arms, and the adaptive nature allows researchers to efficiently incorporate newly available therapeutics.

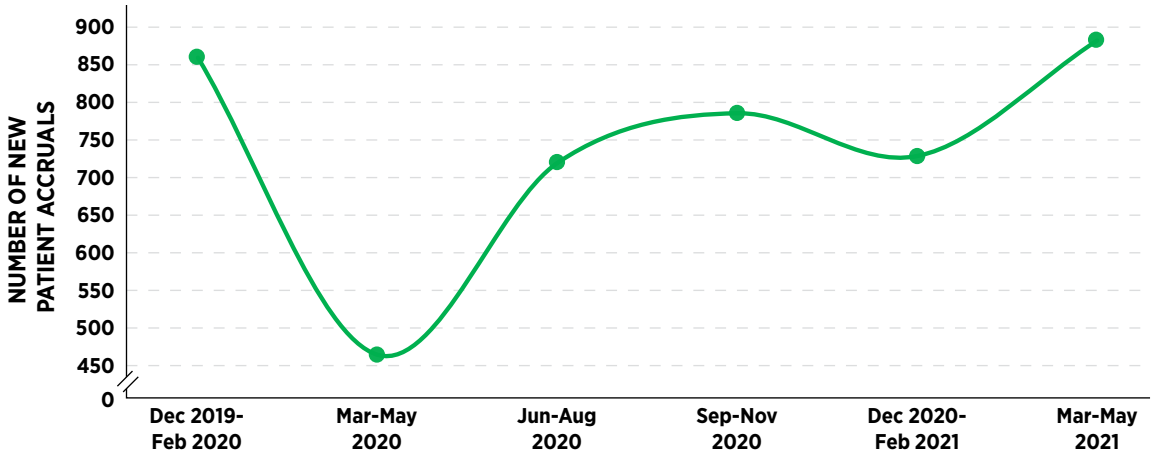
*In some cases, researchers combine different phases into one clinical trial, also called phase I/II or phase III/IV clinical trials depending upon the phases combined, which allows research questions to be answered more quickly or with fewer patients.

†When successful, the results of phase III trials can be used by the U.S. Food and Drug Administration (FDA) to approve new therapeutics or new use of existing therapeutics.

‡Umbrella and basket trials that allow adding experimental arms (for example, if a new targeted therapeutic becomes available against a cancer type being tested in the trial), or removing existing ones (for example if a targeted therapeutic being tested does not prove to be safe and/or efficacious) are also considered platform trials.

Developed from (21,292).

RETURN OF CANCER CLINICAL TRIAL ENROLLMENT TO PREPANDEMIC LEVELS: RESULTS FROM TWO LARGE CANCER CENTERS IN THE U.S. NORTHEAST

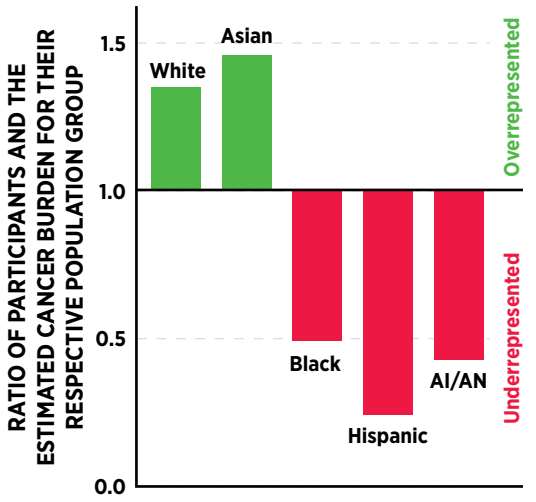


Developed from (294).

who are representative of the U.S. population groups who experience the greatest inequities in the burden of cancer (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?**, p. 13) is essential to accurately extrapolate the safety and efficacy of new treatments to all population groups. Diversity among participants is even more critical to effectively evaluate cutting-edge precision medicine drugs, such as molecularly targeted therapeutics or immunotherapeutics, because these treatments are closely linked to the unique characteristics of an individual's cancer, immune system, and lifestyle, among other factors.

As detailed in the recently released *AACR Cancer Disparities Progress Report 2022*, barriers to participation in clinical trials, especially among racial and ethnic minorities, are numerous, including historical, such as mistrust of the health care system; systemic, such as implicit biases among health care providers; financial, such as cost of the cancer treatment; structural, such as transportation to the study site; and psychological, such as fear of using an experimental drug (13). Overcoming these barriers for all U.S. population groups and addressing the root causes of low participation in clinical trials require concerted and coordinated efforts from stakeholders in the cancer research and care community (see sidebar on **The Medical Research Community: Driving Progress Together**, p. 9).

REPRESENTATION OF U.S. POPULATION GROUPS IN CANCER CLINICAL TRIALS RELATIVE TO THEIR CANCER BURDEN



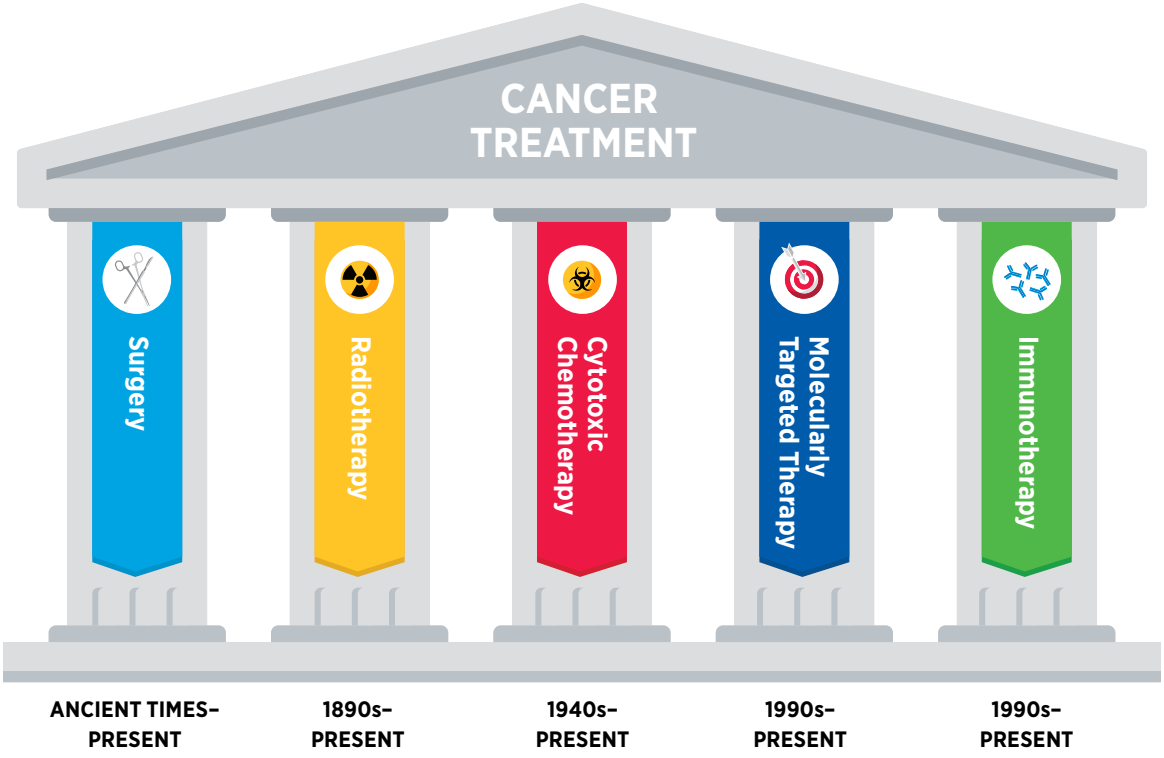
Developed from (295).

Progress Across the Spectrum of Cancer Treatment

Research drives our understanding of how cancer develops mechanistically; how its risk can be reduced proactively; how it can be detected early; how it can be treated effectively; and how it can impact those affected by it differently. This knowledge, in part, leads to FDA approval of new anticancer drugs and medical devices that not only help save more lives, but also accelerate the pace of medical research through new real-world observations (see **Figure 7**, p. 63). The overall goal is to improve outcomes for patients with cancer using—alone or in various combinations—surgery,

FIGURE 8

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 (297). In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar (298). 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 (299). 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 (300). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (301). 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.

chemotherapy, radiotherapy, molecularly targeted therapy, and immunotherapy, the five pillars that constitute the current paradigm for cancer treatment (296) (see **Figure 8**, p. 68).

This section discusses eight new anticancer therapeutics and two new imaging agents approved by FDA during the 12-month period—August 1, 2021, to July 31, 2022—covered by this report. Also highlighted are the 10 previously approved anticancer drugs that were approved by FDA for treating additional types of cancer during the same time (see **Table 4**, p. 69, and **Supplemental Table 2**, p. 164). Not discussed are the previously approved anticancer drugs for which FDA approved either a supplementary dosing schedule or additional uses during treatment of the same cancer type for which they were originally approved, for example, an expansion for treatment at a less advanced stage of the disease.

As we make strides toward effectively treating cancers, it is important to note that not all patients receive and/or benefit from the care recommended for the type and stage of cancer with which they have been diagnosed. Gaps in equitable and affordable access to cancer treatment can result in adverse survival rates that disproportionately affect certain population groups (sidebar on **Disparities in Cancer Treatment**, p. 70). It is

TABLE 4

Newly FDA-approved Anticancer Agents: August 1, 2021-July 31, 2022

Type of Treatment	Generic Name	Trade Name	Mechanism of Action	Approved For
Surgery, Chemotherapy, Radiotherapy	gallium Ga 68 gozetotide	Locametz	Imaging agent	Certain type of prostate cancer
	lutetium Lu 177 vipivotide tetraxetan	Pluvicto	Therapeutic agent	Certain type of prostate cancer
	pafolacianine	Cytalux	Imaging agent	Certain type of ovarian cancer
Molecularly Targeted Therapy	asciminib	Scemblix	Cell-signaling inhibitor	Certain type of leukemia
	belzutifan	Welireg	Cell-signaling inhibitor	Several tumors associated with the von Hippel-Lindau syndrome
	crizotinib	Xalkori	Cell-signaling inhibitor	Certain type of inflammatory myofibroblastic tumors*
	dabrafenib & trametinib	Tafinlar & Mekinist	Cell-signaling inhibitors	Solid tumors carrying certain type of genetic mutation*
	ivosidenib†	Tibsovo	Epigenome-modifying agent	Certain type of bile duct cancer*
	mobocertinib†	Exkivity	Cell-signaling inhibitor	Certain type of lung cancer
	rituximab	Rituxan	Cell-lysis mediator	Certain type of lymphoma*
	sirolimus protein-bound particles	Fyarro	Cell-signaling inhibitor	Certain type of perivascular epithelioid cell tumors*
	tisotumab vedotin-tftv	Tivdak	DNA-damaging agent	Certain type of cervical cancer
	zanubrutinib	Brukinsa	Cell-signaling inhibitor	Certain type of lymphoma*
Immunotherapy	brexucabtagene autoleucel	Tecartus	Immunotherapeutic	Certain type of leukemia*
	ciltacabtagene autoleucel	Carvykti	Immunotherapeutic	Multiple myeloma
	dostarlimab-gxly†	Jemperli	Immunotherapeutic	Solid tumors with a specific genetic feature*
	relatlimab-rmbw	Opdualag	Immunotherapeutic	Certain type of melanoma
	tebentafusp-tebn	Kimmtrak	Immunotherapeutic	Certain type of ocular melanoma
	tisagenlecleucel	Kymriah	Immunotherapeutic	Certain type of lymphoma*

*New cancer type approved 2021-2022

†Requires a companion diagnostic

essential for stakeholders across the cancer research continuum to address these disparities urgently and collectively if the vision of cancer health equity is to be realized.

ADVANCES IN CANCER TREATMENT WITH SURGERY

Surgery can be used in several ways during the care of a patient with cancer (see sidebar on **Using Surgery for Cancer Treatment**, p. 71). For centuries, surgery was the only available cancer treatment and remains an important treatment option for many patients (see **Figure 7**, p. 63).

According to a recent study, more than nine million patients globally needed surgery for treatment of their cancer in 2018—researchers estimate this number to increase by five million by 2040 (307).

Despite the rapid pace of development and approvals of molecularly targeted therapies and immunotherapies in recent decades, the use of surgery in cancer care, especially alongside one or more classes of therapies available for the diagnosed cancer type, remains common. The goal of combining surgery with other classes of therapies is to eliminate any cancer cells that surgery might not remove. For many cancer patients, a multidisciplinary team of medical professionals including those specialized in

Disparities in Cancer Treatment

Discovery science is constantly fueling the development of new cancer treatments. However, several segments of the U.S. population remain at a disadvantage to fully benefit from the recommended cancer treatments. Findings of selected recent studies evaluating persistent disparities across the five pillars of cancer treatment are listed below:

SURGERY

American Indian or Alaska Native patients with kidney cancer were 49 percent more likely than White patients to undergo complete surgical removal of the kidney, a procedure associated with higher mortality rates (302).

RADIOTHERAPY

Native Hawaiian or Other Pacific Islander women with early-stage breast cancer were more likely than White women to experience a delay of 10 days following cancer surgery to receive radiation (303).

CHEMOTHERAPY

Black women with breast cancer living in rural South Carolina were two times more likely than White women to experience delays in recommended chemotherapy (304).

MOLECULARLY TARGETED THERAPY

Black patients with lung cancer were more likely than White patients to experience a delay of 28 days to receive a prescription for one of the FDA-approved molecularly targeted therapeutics (305).

IMMUNOTHERAPY

Hispanic patients with metastatic liver cancer were 37 percent less likely than White patients to receive immunotherapy (306).

performing surgery, administering radiation, and treating the diagnosed cancer, as well as other individuals as appropriate (e.g., nurses, social workers), reviews treatment options and makes an expert recommendation for treatment with the goal to maximize the benefit and minimize harms from surgery.

Sometimes, additional therapy is given before, after, or around the time of surgery based on specifics of the situation (see sidebar on **Commonly Used Terms and Benchmarks in Clinical Studies**, p. 72). Researchers have found that this approach not only improves the surgeon's ability to remove the tumor (for example by shrinking the tumor when given before the surgery), but also increases the patient's overall survival and/or quality of life (308).

Visualizing Ovarian Tumors Precisely During Surgery

Ovarian cancer is the number five cause of cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. According to recent estimates, nearly 20,000 women will be diagnosed with ovarian cancer and more than 12,000 will die because of ovarian cancer in the U.S. 2022 (1).

Research has revealed that a complete surgical removal of ovarian cancer following standard-of-care chemotherapy increases overall survival by nearly 14 months (309). Surgeons have thus far relied on either imaging tumors before surgery, visually inspecting tumors under normal light during surgery, or examining tumors by touch to identify cancerous tissue, all of which are imprecise methods. In November 2021, FDA approved pafolacianine (Cytalux)—the first tumor-targeted imaging agent for ovarian cancer—to assist surgeons in visualizing hard to detect lesions in adult patients with ovarian cancer during the surgery.

Pafolacianine is given via an intravenous injection between one and nine hours before surgery. The fluorescent agent binds to the folate receptor, a protein which is present in abundance on the surface of ovarian cancer cells (310). Ovarian cancer cells, with the imaging agent bound to folate receptor on their surface, are then visualized during surgery using a Near-Infrared fluorescence imaging system, which was simultaneously approved by FDA specifically for use with pafolacianine.

FDA approval of pafolacianine was based on a randomized clinical trial that evaluated the safety and efficacy of the imaging agent in women who were diagnosed with ovarian

Using Surgery for Cancer Treatment

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

- **Surgery to diagnose cancer** is performed to obtain a tumor sample for diagnosing cancer.
- **Surgery to stage cancer** is performed to determine how far the cancer has spread from the site of origin so that the best treatment plan can be developed for the patient.
- **Surgery to cure cancer** is performed to remove the entire tumor if cancer is confined to one area of the body.
- **Surgery to debulk cancer** is performed to remove only part of the tumor if it is very large and/or located very close to important organs or tissues.
- **Surgery to ease problems caused by cancer** is performed to remove tumors that are causing pain, pressure, or blockages in patients with advanced-stage cancer.

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

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

Minimally invasive surgery is when a surgeon makes one or more small cuts to remove the tumor and some surrounding healthy tissue using special surgery tools with assistance from specialized devices, such as a long, thin tube with a tiny camera, that allow the surgeon to see what is happening.

cancer or had high likelihood of having ovarian cancer and were scheduled to undergo surgery (311). A dose of the imaging agent was given to 134 women (ages 33 to 81). When evaluated under both normal and fluorescent light during surgery, pafolacianine detected in 27 percent of women at least one cancerous lesion that was not observed by standard visual inspection. Approval of pafolacianine is expected to substantially improve ovarian cancer surgery by enhancing a surgeon's ability to find otherwise undetectable ovarian lesions.

IMPROVEMENTS IN RADIATION-BASED APPROACHES TO CANCER CARE

Radiotherapy is the use of high-energy rays (e.g., gamma rays and X-rays) or particles (e.g., electrons, protons, and carbon nuclei) to control or eradicate cancer. Discovery of X-rays in 1895 allowed visualization of internal organs at low doses and the effective use of X-rays at high doses to treat a breast cancer patient a year later established radiotherapy as the second pillar of cancer treatment (see **Figure 8**, p. 68). Radiotherapy plays a central role in the management of cancer and works primarily by damaging DNA, leading to cancer cell death. The use of radiotherapy in treatment and management of cancer continues to increase, as indicated by a 16.4 percent increase in radiation facilities across the U.S. between 2005 and 2020 (312).

There are many types and uses of radiotherapy (see sidebar on **Using Radiation in Cancer Treatment**, p. 73). However, it is important to note that radiotherapy may also have harmful side effects, partly because of the radiation-induced damage to cells in healthy organs surrounding the tumor tissue (313). Researchers are continuously working on making radiotherapy safer and more effective and designing novel radiotherapeutics (alone or in combination) to target more cancer types and benefit more patients. Recent technological advances, such as the development of sophisticated computer analytic programs assisted by AI, are helping optimize the delivery of the radiation to the tumor while minimizing exposure to normal tissues (314).

Delivering Radiation Precisely to Metastatic Prostate Cancer

One of the most exciting areas of research in radiotherapy is theragnostics (315). Theragnostics, also called theranostics, is a treatment approach in which cancer is visualized by positron emission tomography (PET) or computer tomography (CT) imaging using molecules that are linked to weak radionuclides and bind to specific proteins on the surface of cancer cells. Once the presence of cancer is confirmed, the same targeting agents—labeled with more potent radioactive compounds—are then used to kill cancer cells. Breakthrough advances in this area are reflected by the recent FDA approvals, highlighted

Commonly Used Terms and Benchmarks in Clinical Studies

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
A statistics term. The middle value in a set of measurements. For example, the length of time from either the date of cancer diagnosis or the start of treatment that half of the patients in a group of patients diagnosed with the disease are still alive.

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

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

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

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

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

PROGRESSION-FREE SURVIVAL
Time from start of the clinical study until disease progression or death.

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

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

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

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

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

in the *AACR Cancer Progress Reports 2018* and *2021* (21,316) and discussed below, of a radiodiagnostic agent and a radiotherapeutic agent for the visualization and treatment of metastatic castrate-resistant prostate cancer (mCRPC).

Prostate cancer is the most diagnosed cancer, after non-melanoma skin cancer, and is the second leading cause of cancer deaths after lung cancer in U.S. men (1). Early-stage prostate cancer cells rely on normal levels of testosterone to proliferate. Although not routinely used, one of the treatment strategies for early-stage prostate cancer is to inhibit androgen receptor activity, which helps lower testosterone to very low levels and thus slows cancer growth. However, some advanced-stage prostate cancer cells treated with anti-androgen therapy adapt to become independent of testosterone and continue to proliferate, and often spread to other organs even when the testosterone levels in the body are very low. This type of prostate cancer is called metastatic castrate-resistant prostate cancer (mCRPC) and can be very difficult to treat.

In March 2022, FDA approved lutetium Lu 177 vipivotide tetraxetan (Pluvicto), referred as ^{177}Lu-PSMA-617, for the treatment of adult mCRPC patients who have been treated with a combination of androgen receptor inhibition and chemotherapy,

Using Radiation in Cancer Treatment

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

TREATMENT OF CANCER

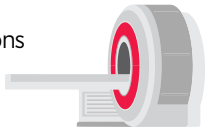
Radiotherapy, or radiation therapy, uses high-energy radiation to control and eliminate the disease.

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 conformational radiotherapy (3DCRT)** delivers high-energy X-rays via multiple beams that, with the help of computed tomography and/or magnetic resonance imaging, more precisely 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.
- **Intraoperative radiation therapy** delivers electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures.
- **Stereotactic radiotherapy** delivers radiation to very well-defined smaller tumors, typically using more than eight beams with the help of a highly sophisticated imaging system. It is used in both stereotactic surgery (to treat tumors of the brain and central nervous system) and stereotactic body radiotherapy (to treat small tumors within larger organs of the body).

Particle therapy
Delivers higher doses of protons or carbon ions, instead of X-rays, to the tumor and causes less damage to surrounding tissue because the heavier particles used 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 selected patients is still being determined.

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, particularly small and locally advanced cancers; it is often used in combination with systemic therapy.

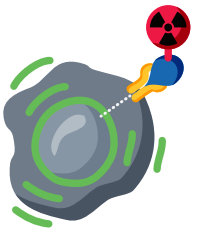
Neoadjuvant radiotherapy
Used to shrink a tumor so that it can be subsequently treated by a different method such as surgery.

Adjuvant radiotherapy
Used to eliminate any remaining cancer following prior treatment.

Palliative radiotherapy
Used to reduce or control symptoms of disease when cure by another method is not possible.

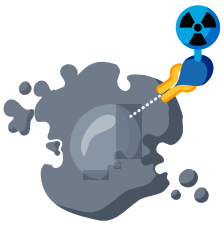
Salvage radiotherapy
Used to treat cancer after the cancer has not responded to other treatments.

TARGETING PROSTATE CANCER



FDA APPROVED

to visualize cancer cells
DIAGNOSTIC AGENT
gallium Ga 68 gozetotide
(Locametz)



FDA APPROVED

to kill cancer cells
THERAPEUTIC AGENT
lutetium Lu 177
vipivotide tetraxetan
(Pluvicto)

and whose cancer cells have a protein called prostate-specific membrane antigen (PSMA) on their surface. Concurrently, FDA approved gallium Ga 68 gozetotide (Locametz), also called ^{68}Ga-PSMA-11, which is the first radioactive diagnostic agent approved for the selection of patients for radiotherapy.

The FDA approval of both agents was based on a clinical trial in which patients with previously treated mCRPC first received radiodiagnostic agent ^{68}Ga-PSMA-11, a weak radionuclide that binds to PSMA protein on the surface of prostate cancer cells (317). Patients in which PET imaging detected at least one tumor lesion with ^{68}Ga-PSMA-11 were selected for treatment with the radiotherapeutic agent ^{177}Lu-PSMA-617, which also binds to PSMA but is a much stronger radionuclide. Of 831 PSMA-positive mCRPC patients who fulfilled the requirements of the study, 551 patients received both the best standard of care (BSoC) and ^{177}Lu-PSMA-617 every six weeks for up to a total of six doses; the remaining 280 patients received BSoC alone. Findings of the study showed an increase of 5.3 months in progression-free survival and an increase of 4.0 months in overall survival among patients who received the radiotherapeutic and BSoC compared to those who only received BSoC (317) (see sidebar on **Commonly Used Terms and Benchmarks in Clinical Studies,** p. 72).

These improvements mark a significant progress against an advanced-stage, difficult-to-treat cancer and provide hope for mCRPC patients, who otherwise have limited treatment options. Researchers are also actively working on developing additional theragnostic agents for the treatment of metastatic prostate cancer (318).

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

As with surgery, chemotherapy is more commonly being used to treat cancer in combination with one or more types of therapies. Furthermore, FDA continues to grant approvals to newer and more effective chemotherapeutics. FDA routinely expands the use of previously approved chemotherapeutics to treat patients with subtypes of the same cancer for which the chemotherapeutic was previously approved (for example, the approval in May 2022 of azacitidine [Vidaza] to treat pediatric patients with juvenile myelomonocytic leukemia). Many FDA approvals of chemotherapeutics are in combination with other previously approved targeted therapies (for example, the approval in December 2021 of chemotherapy to be used in combination with a molecularly targeted therapeutic rituximab [Rituxan] to treat certain types of childhood blood cancer). In addition, FDA approves new formulations of previously approved chemotherapeutics (for example, the approval in September 2020 of a new formulation of azacitidine [Onureg] that could be taken orally allowing patients with acute myeloid leukemia to continue their medication in the midst of the COVID-19 pandemic without needing to visit a clinic).

ADVANCES IN TREATMENT WITH MOLECULARLY TARGETED THERAPY

Discovery science has played a key role in unraveling the complexities of cancer and in providing a deeper understanding of the numerous genetic mutations that drive cancer development. As a result, recent decades have seen major advances in precision medicine. Cancer patients now have many treatment options that are specific to the genetic changes driving their cancer, or based on the characteristics of their cancer type. These anticancer agents—called molecularly targeted therapeutics—target cancer cells within a tumor more precisely, making the treatment more effective and less toxic than cytotoxic chemotherapy. Thus, molecularly targeted therapeutics are not only saving the lives of cancer patients, but are also leading to a higher quality of life for cancer survivors after treatment.

Adding Precision to the Treatment of Rare Cancers

According to NCI, a cancer is considered rare if it affects fewer than 15 per 100,000 people every year (319). Of all the various cancer types, 27 percent are considered rare, including all childhood cancers. Because of the rarity of these cancers, it is harder for the patient to find a provider who is an expert in treating the rare cancer with which the patient is diagnosed, and it is harder for researchers to obtain biospecimens to learn about the cancer or find enough participants for clinical trials to test new treatments.

Despite the challenges, there have been significant advances in recent decades toward treating rare cancers, as highlighted by the FDA approvals covered in this report. These approvals include new or improved treatment options for cancers that are caused by a rare inherited cancer syndrome; for a family of rare soft tissue tumors; and for bile duct cancer.

The von Hippel-Lindau (VHL) syndrome is a rare, inherited disorder that is caused by a mutation in the *VHL* gene. It is estimated that between 3,000 and 30,000 people in U.S. have VHL syndrome (1). Patients with VHL disease have an increased risk of developing certain types of cancer, especially kidney cancer and pancreatic cancer, and thus far, the treatment options for patients with VHL syndrome have been limited to surgery and/or radiotherapy.

In August 2021, FDA approved belzutifan (Welireg) for adult patients who have several tumors associated with VHL disease that do not require immediate surgery. Specifically, the drug is approved to treat VHL-associated renal cell carcinomas (a type of kidney cancer), central nervous system hemangioblastomas (tumors that arise from the linings of blood vessels), or pancreatic neuroendocrine tumors (tumors of specialized cells called neuroendocrine cells that have the properties of both nerve- and hormone-producing cells, and regulate important body functions, such as blood flow).

Belzutifan is an inhibitor of hypoxia-inducible factor, a protein that functions as an oxygen sensor and helps cancer cells grow in low oxygen conditions that are a characteristic of the tumor microenvironment (see **The Blood System**, p. 24) (320). The FDA approval of belzutifan was based on results from a small clinical trial that tested the drug in patients with VHL-associated renal cell carcinoma; all of the patients also had other VHL-associated primary tumors (321). After 18 months, kidney tumors in 49 percent of the patients shrank at least 30 percent, and tumors in a majority of the patients were still responding after one year. Belzutifan also shrank VHL-associated brain, pancreatic, and eye tumors in 30 percent, 77 percent, and 100 percent of patients, respectively. Belzutifan is the first FDA-approved drug for the treatment of patients with VHL-associated tumors such as **Alexandra Vitale** (see p. 76) (321).

Perivascular epithelioid cell tumors, also called PEComas, are a family of very rare tumors that form in the soft tissues of the stomach, intestines, lungs, female reproductive organs, and genitourinary organs. The tumors occur in about one case per million people, often in children with an inherited condition called tuberous sclerosis. It is estimated that there are about 100 to 300 new patients per year in the U.S. Most perivascular epithelioid cell tumors are benign (not cancerous), however patients with malignant PEComas have a very poor outcome, with median survival of only 16 months after treatment with chemotherapy (322).

In November 2021, FDA approved sirolimus protein-bound particles as an injectable suspension (Fyarro) for adult patients with malignant PEComa that cannot be removed surgically or has spread to other organs. Sirolimus is a chemical compound that inhibits activity of the mechanistic target of rapamycin (mTOR), a protein important for cell division and survival (323). In the formulation newly approved by FDA, sirolimus is bound to albumin, which is a common protein present in blood and soluble in water. Efficacy of the approved drug was evaluated in 31 patients with malignant PEComa that had spread to other organs or could not be removed by surgery. Thirty-nine percent of patients responded to the treatment, including two patients who had complete remission. Among the patients who responded, 67 percent and 58 percent had a response that lasted more than 12 months and 24 months, respectively (324).

Cells use glucose as a primary source of energy to divide and perform other essential functions. Cells convert glucose into fuel through a series of steps, each of which is controlled by essential proteins, or enzymes. Isocitrate dehydrogenase (IDH) is one such protein, and the cells have two closely related forms of IDH—IDH1 and IDH2 (325).

Research has revealed that IDH1/2 proteins are modified in certain cancers, such as those of the blood, brain, and bile duct (326). Modifications in IDH1/2 proteins cause cancer cells to acquire changes in their epigenome (see **Epigenetic Changes**, p. 24), that help them divide faster than normal cells (327). Development of molecularly targeted therapeutics against the modified forms of IDH1/2 is an exciting area of research (328).

Cholangiocarcinoma is a group of cancers that begin in the bile ducts, which are the tubes that connect liver and gallbladder to small intestine. Cholangiocarcinomas, or bile duct cancers, are rare and affect about 8,000 Americans every year (1). Bile duct cancers are associated with poor outcomes for patients both at early and advanced stages of the disease. About 10 percent of bile duct cancers carry mutations in *IDH1/2* genes (326).

In August 2021, FDA approved ivosidenib (Tibsovo) for adult patients with cholangiocarcinoma who were previously treated, had locally advanced or metastatic disease and an IDH1 mutation. FDA also approved the Oncomine Dx Target Test as a companion diagnostic to detect IDH1 mutation for selecting patients for treatment with ivosidenib.

Ivosidenib, an inhibitor of the mutated form of IDH1, was approved based on findings of a phase III clinical trial that evaluated the efficacy of the drug in 187 patients (329). Patients were randomly assigned to receive ivosidenib or placebo (see sidebar on **Commonly Used Terms and Benchmarks in Clinical Studies**, p. 72). Initial findings from the study reported that ivosidenib treatment nearly doubled progression-free survival (2.7 months in the ivosidenib group versus 1.4 months in the placebo group) (330). Subsequent findings from the clinical trial revealed that the overall survival doubled in patients treated with ivosidenib (10.3 months in the ivosidenib group versus 5.1 months in the placebo group) (329). The expanded use of ivosidenib—previously approved by FDA in 2018 to treat acute myeloid leukemia patients with IDH1 mutation—brings hope for patients with an aggressive form of cancer, for which there are limited treatment options.

In July 2022, FDA approved crizotinib (Xalkori) to treat adult and pediatric patients (1 year of age and older) who have inflammatory myofibroblastic tumors (IMT) that have returned or have become resistant to other cancer treatments and cannot be surgically removed. The approval is specifically to treat patients whose IMT have alterations in the gene for anaplastic lymphoma kinase (ALK); these alterations increase the activity of the enzyme, which helps cancer cells divide faster. Crizotinib was first approved to treat lung cancer with alterations in the *ALK* gene in 2011.

Continued on page 78

A New Lease on Life, Thanks to a Breakthrough Treatment

When Alexandra was five years old, her parents noticed that her left eye was weaker than her right eye.

At the Wills Eye Institute in Philadelphia, ophthalmologists found a benign tumor on her optic nerve. After laser surgery to remove the tumor, genetic tests revealed that Alexandra had von Hippel-Lindau (VHL) disease, a rare inherited condition characterized by the formation of both benign and malignant tumors in different parts of the body.

"Anywhere from the eyes, ears, central nervous system, endocrine system, kidneys, you name it, I've probably had it," she said.

When Alexandra turned 20, the incidence of tumors increased, and she underwent MRI scans every three to six months for surveillance.

"Every time I went back for a scan, a new tumor was detected seemingly out of nowhere, even though I wasn't having any symptoms," she said.

In 2011, Alexandra developed benign tumors on her adrenal glands that necessitated surgery.

Then, four years later, in 2015, scans revealed that she had developed renal cell carcinoma—the most common form of kidney cancer—as well as malignant tumors in her pancreas. This led to a major surgery called pancreaticoduodenectomy, more commonly known as the Whipple procedure. At the same time, Alexandra had a partial nephrectomy to remove the tumors in her kidney.

"That was probably the worst surgery I've ever been through," she said. "The Whipple was probably one of the hardest ones to recover from."

Eight months later, scans found a tumor on her cerebellum that also required yet another surgery.

"Weirdly enough, that was actually an easier surgery to recover from than the Whipple," she said.

In December of 2018, Alexandra developed another small tumor on her kidney, which qualified her to participate in a small open-label clinical trial. The study involved just 50 VHL patients who had at least one renal cell carcinoma tumor to test a therapeutic designated as PT2977, and now known as belzutifan (Welireg).

"I remember getting the phone call and being ecstatic, crying on the phone just at the thought of being able to participate in this trial," Alexandra said.

Alexandra had—and continues to have—a good response to belzutifan.

"On this medicine, my tumors have either remained stable, or shrunk to the point where some of them can't even be measured," she said. "This drug is a reset on my life and that's the best way to explain it. Mentally, physically, I am better now probably than I ever have been."

In August 2021, based on the results of the trial Alexandra participated in, the U.S. Food and Drug Administration (FDA) approved belzutifan for patients with VHL-associated solid tumors.

The development of drugs, such as belzutifan, is driven by basic science discoveries made possible through federal funding of medical research.

"Funding cancer research as much as possible will give people like me more time with loved ones. That is true for me, that is true for you, and that is true for members of Congress," she said. "Everyone has been exposed to someone or knows someone who has been diagnosed with cancer. Why wouldn't we put our money into it?"

Alexandra no longer dreads the MRI scans she continues to undergo on a regular basis.

"I'm actually excited reading the MRI reports because I look forward to seeing if tumors have shrunk and if they are stable," she said. "That's because, for the bulk of my life, I wasn't hearing anything along the lines of stable or shrinkage."

Through the many years living with VHL and the surgeries, scans, and other treatments associated with the disease, Alexandra was supported by her parents, her little brother, and her partner of seven years, Shelby.

Alexandra takes belzutifan daily–three pills that she takes in the evening because it can cause her nausea—and is scanned every three months to monitor her tumors. She remains extremely optimistic about the future thanks to the medication that has kept her cancer in check.

"I've been telling myself for my entire life, 'You have to stay positive and continue to move forward,' And quite honestly, that's just a message that everyone and anyone can follow."

"We're in 2022. I haven't had a surgery since 2017. That's a big feat for me. We have to keep finding new treatments, because there are a lot of others out there like me that need a real chance at life, and a drug like this is just life-changing."

ALEXANDRA VITALE • AGE 31 • TOWNSEND, DE

Photo © Dean Tatulli

IMT is a very rare and usually benign (noncancerous) tumor. An estimated 150 to 200 people are diagnosed with IMT in the U.S. annually. IMT forms in tissues called mucosal surfaces and mesentery, and primarily develops in children and young adults. Mucosal surfaces are found in eyes, nose, mouth, digestive tract, lungs, and genital and urinary tracts. Mesentery connects the organs in the abdomen. IMT contains a lot of immune cells, making the tumor look "inflamed" like an infection. IMT can cause many issues for patients as it can grow in the way of important organs such as the lung or stomach and, in very rare cases, can spread to distant organs. Recent studies have shown that about 50 percent of IMT tumors carry alterations in the ALK gene (331,332).

FDA approval of crizotinib, which inhibits the activity of ALK protein, to treat patients with IMT was based on findings of two small clinical studies, one with 14 pediatric participants with IMT and the second with seven adult participants with IMT. A total of 12 of the pediatric patients and five of the seven adult patients partially or completely responded to the treatment (333). The approval expands the treatment options of this rare cancer type.

According to NCI, a quarter of all cancer deaths in the U.S. each year are due to rare cancers (319), making rare cancers a major public health challenge and a key priority for NCI (see sidebar on **National Cancer Institute Initiatives to Understand and Treat Rare Cancers**, p. 78). FDA approvals of the drugs discussed in this section, as well as the new immunotherapeutics to treat certain forms of rare cancers (see **Advances in Cancer Immunotherapy**, p. 87), address a key unmet need in cancer care and signal major advances toward treating rare cancers.

Expanding Treatment Options for Patients with Blood Cancers

Leukemia is a type of blood cancer that begins in the bone marrow and moves into blood as cancer cells proliferate and overcrowd the cavity inside the bone where the bone marrow resides.

Chronic myeloid leukemia (CML) is a slow-growing cancer of myeloid cells. CML is characterized by the presence of a structural genetic variation in which pieces of chromosomes 9 and 22 break off and trade places. As a result, the *ABL* gene

National Cancer Institute Initiatives to Understand and Treat Rare Cancers

Recognizing the challenges of studying rare cancers and developing treatment against them, NCI is leading several initiatives to facilitate mechanistic understanding of rare cancers, as well as to develop approaches that expedite development and testing of new treatments against these diseases. Some of these initiatives are listed below:

NIH NATIONAL CANCER INSTITUTE

INTERNATIONAL RARE CANCER INITIATIVE (IRCI)

Established in 2011 by NCI, the UK National Institute for Health Research, Cancer Research UK, and the European Organisation for Research and Treatment of Cancer, later joined by the French National Cancer Institute, the Canadian Clinical Trials Group, the Japan Clinical Oncology Group, and the Clinical Oncology Society of Australia—is aimed at conducting practice-changing clinical trials for patients with rare cancers.

NCI RARE TUMOR INITIATIVE

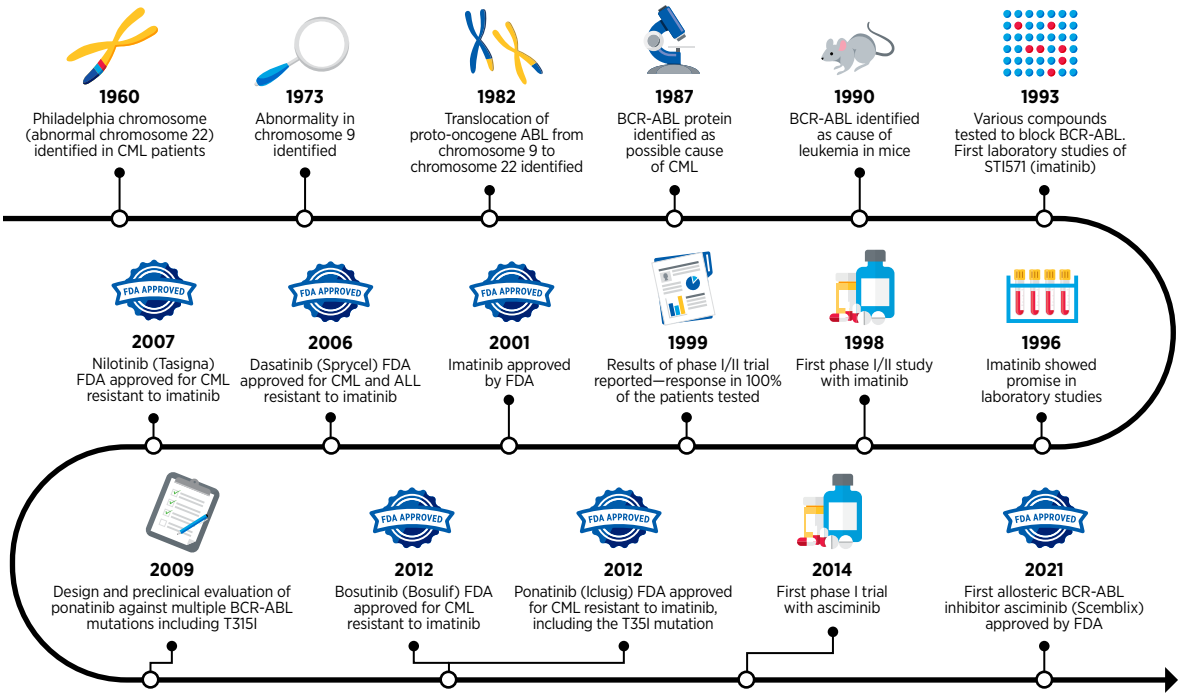
Launched in 2013—is aimed at fostering closer collaborations between basic and clinical scientists, patient advocacy groups, and industry partners to facilitate the development of new approaches to treating patients with rare cancers.

RARE TUMOR PATIENT ENGAGEMENT NETWORK

Initiated in 2016 by the NCI Center for Cancer Research as part of the Cancer Moonshot—is aimed at studying selected rare pediatric and adult tumors and developing a network of clinical trials. Finding treatments for childhood, teen, and young adult rare solid tumors is the focus of the My Pediatric and Adult Rare Tumor (MyPART) network, while the NCI Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI-CONNECT) is studying 12 rare central nervous system cancers in adults.

FIGURE 9

The Pathway to Progress Against Chronic Myelogenous Leukemia



Development of the first molecularly targeted therapy approved by the U.S. Food and Drug Administration (FDA)—imatinib (Gleevec)—was the culmination of numerous groundbreaking discoveries. The story began in 1960, when a multi-institutional collaborative team of researchers noted that the majority of patients with chronic myelogenous leukemia (CML) had an abnormal chromosome 22, which was called the Philadelphia chromosome (named because it was discovered at research institutes located in Philadelphia, Pennsylvania). In 1973, the abnormal chromosome 9 was discovered and, in 1980, it was discovered that two chromosomes traded pieces to generate an entirely new protein, BCR-ABL, the activity of which was later found to cause CML. As a result, drugs that shut off the BCR-ABL functions by blocking the most active sites within the protein were developed.

Clinical trials for many of the drugs, including imatinib, began in 1998, subsequently resulting in FDA approval of imatinib for the treatment of Philadelphia chromosome–positive CML in 2001. Subsequently, identification of imatinib-resistant patients led to the development and FDA approval of dasatinib (Sprycel) in 2006, nilotinib (Tasignia) in 2007, and bosutinib (Bosulif) in 2012. However, none of these drugs were effective against the T315I BCR-ABL mutation. In late 2012, the FDA approved ponatinib (Iclusig) for the treatment of T315I-mutant CML. Since its approval, ponatinib has benefited many patients; however, its success in treating patients whose CML cells have acquired the highly resistant T315I BCR-ABL mutation has been greatly varied.

In October 2021, FDA approved asciminib (Scemblix), the first BCR-ABL inhibitor that binds to a different active site of the protein than any of the drugs indicated above, and persistently blocks the activity of the mutated form of BCR-ABL.

from chromosome 9 joins the *BCR* gene on chromosome 22 to form an entirely new and abnormal gene called *BCR-ABL*. The structurally altered chromosome 22 with the *BCR-ABL* gene is called the Philadelphia chromosome and is present in more than 90 percent of all CML (also called Philadelphia positive or Ph+ CML) patients (see **Figure 9**, p. 79). The *BCR-ABL* gene makes the BCR-ABL protein, which makes the cancer cells proliferate faster than normal myeloid cells (334).

It is estimated that 8,860 new cases of CML will be diagnosed in the U.S. in 2022, and 1,220 people will die from it (1). Patients with Ph+ CML have several treatment options available, and typically respond well to therapies that are targeted against the BCR-ABL protein (see **Figure 9**, p. 79). However, in some cancer cells, the *BCR-ABL* gene acquires additional mutations or doubles in number, thus conferring resistance against the existing therapies and posing a challenge to successful treatment of the disease (see sidebar on **The Challenge of Treatment Resistance**, p. 80).

In October 2021, FDA granted accelerated approval to asciminib (Scemblix) for Ph+ CML patients whose cancer is in a chronic phase, i.e., when cancer cells account for less than 10 percent of the total number of cells in bone marrow or blood samples, and who have been previously treated with two or more inhibitors of tyrosine kinases. Tyrosine kinases, such as ABL, belong to a large family of specialized proteins, called enzymes, and play critical roles in cell proliferation, differentiation, and identity (335). FDA also approved asciminib for adult patients with Ph+ CML, whose cancer is in a chronic phase and who have the T315I mutation in the BCR-ABL protein (see **Figure 10**, p. 81).

FDA approval was based on findings from two clinical trials; in one study, 233 patients were randomly assigned to receive either asciminib or bosutinib—the BCR-ABL inhibitor that was approved by FDA in 2012 to treat Ph+ CML (336). Patients were evaluated at 24 weeks for major molecular response, which means that the number of Ph+ CML cells in blood or bone marrow—as assessed by a molecular test—is 1/1000th or less of what is expected in a CML patient who has not been treated. Major molecular response was 25 percent in patients treated with asciminib compared to 13 percent in patients who received bosutinib.

The second clinical trial evaluated the efficacy of asciminib in patients with Ph+ CML who also had the T351I mutation (337). Major molecular response was achieved in 42 percent of the patients by 24 weeks, and in 49 percent of the patients by 96 weeks. Importantly, the response lasted for more than two years, indicating that asciminib is highly effective in treating Ph+ CML patients who have developed resistance to other available molecularly targeted therapies.

The approval of asciminib is a major advance toward successfully treating Ph+ CML patients who develop resistance to currently available treatments and face significantly worse outcomes.

B cells are a type of white blood cells in the immune system that make antibodies to help the body defend against foreign substances, such as toxins, and pathogens, such as viruses. Antibody production by B cells is, in part, regulated by a tyrosine kinase, called Bruton's tyrosine kinase (BTK) (338). As mentioned above, tyrosine kinases are specialized proteins that catalyze many important chemical reactions in the cell and regulate critical cellular functions, such as cell proliferation, differentiation, and identity (339). In normal B cells, BTK is only active when the body needs additional B cells and/or antibodies. However, in cancers of B cells, mutations in the *BTK* gene result in chronic activation of the BTK protein. The mutated BTK helps cancer cells to divide and the tumors to grow faster than normal cells, and has become an attractive target for development of molecularly targeted therapeutics to treat cancers of B cells (340).

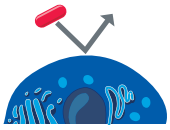
In August 2021, FDA expanded the use of zanubrutinib (Brukinsa)—an inhibitor of BTK originally approved in 2019

The Challenge of Treatment Resistance

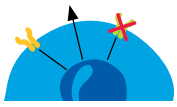
Diversity, or heterogeneity, among cancer cells within and between tumors is a major cause of treatment resistance. Some examples of heterogeneity are as follows:

Some cancer cells in a tumor may not be rapidly dividing, thus becoming insensitive to treatments that target rapidly dividing cells, such as cytotoxic chemotherapeutics.

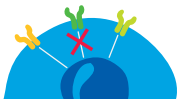
Some cancer cells in a tumor may have or may acquire mutations in the target against which the drug is developed, thus rendering the treatment ineffective.



Some cancer cells in a tumor may have or may acquire molecular or cellular differences other than changes in the treatment target, thus rendering the treatment ineffective.



Some cancer cells in a tumor may leverage redundancies in signaling networks that help them proliferate uncontrollably, thus becoming resistant to a treatment targeting a signaling protein.

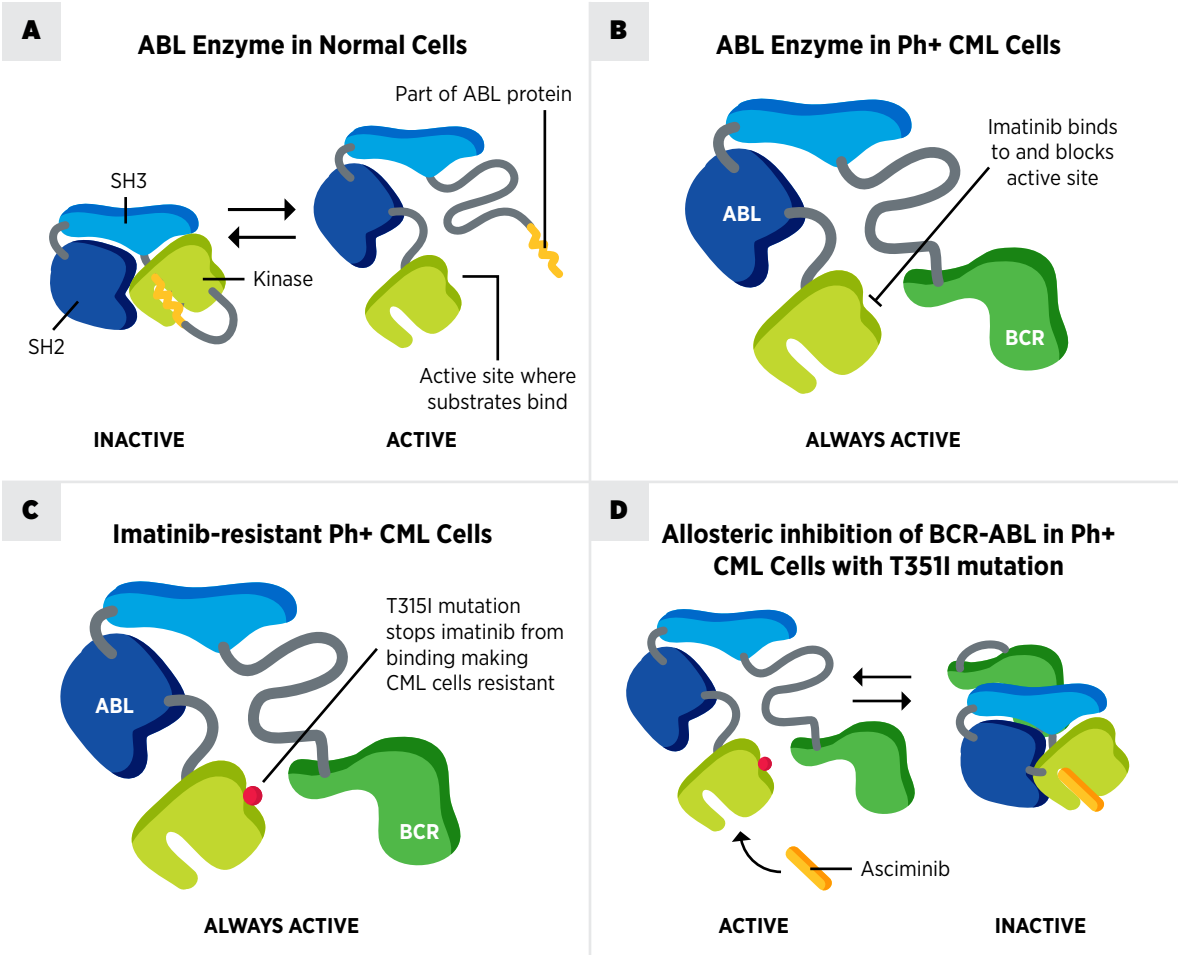


In addition, differences in tumor microenvironmental components can render a treatment ineffective.

Adapted from (21).

FIGURE 10

How Does Asciminib Work?



In normal cells, the activity of the ABL enzyme is regulated by cues from outside the cell. Typically, ABL enzyme is present in normal cells in an inactive form, in which one part of the protein is "locked" into another part of the protein as a "key" and prevents substrates from binding to the enzyme. When a cell receives cues to perform certain functions, such as divide, the ABL enzyme acquires an active form which allows substrates to bind to the enzyme, ultimately helping cells proliferate (**Panel A**).

In Philadelphia chromosome positive (Ph+) CML cells, the portion of the ABL protein that controls the self-regulation is replaced by the BCR protein, thus keeping the ABL enzyme in an active form at all times. As a result, Ph+ CML cells divide and proliferate uncontrollably. The drug imatinib (Gleevec) inhibits the activity of the ABL protein even when the "lock and key" mechanism that keeps the ABL protein inactive in normal cells is lost in Ph+ CML cells (**Panel B**).

Unfortunately, the BCR-ABL protein in Ph+ CML cells acquires mutations, such as T315I, that prevent imatinib from binding to and inhibiting the activity of the protein, thus making the cancer cells resistant to treatment with imatinib (**Panel C**).

Asciminib utilizes the naturally occurring "lock and key" mechanism to inactivate BCR-ABL protein, thus overcoming the imatinib resistance of Ph+ CML cells and restoring inhibition of BCR-ABL1 kinase activity (**Panel D**).

Developed from (337).

to treat another rare form of blood cancer called mantle cell lymphoma—to treat adult patients with Waldenström macroglobulinemia (WM).

WM begins in B cells and is a rare type of non-Hodgkin lymphoma. Each year, an estimated 1,000 to 1,500 U.S. adults are diagnosed with WM (1). Cancer cells in patients with WM make a large amount of a certain type of antibody called macroglobulin. The buildup of this protein in the body can lead to excess bleeding, problems with vision, and problems with the nervous system (341).

WM typically develops in adults older than 70 years and grows slowly in most patients. Although several molecularly targeted therapeutics have received FDA approval in recent years for treatment of WM, patients often develop resistance to the existing therapies and the disease can still progress to more aggressive lymphoma, underscoring the continued need to develop newer and better therapeutics against the disease.

The FDA approval of zanubrutinib to treat adult patients with WM was based on a phase III clinical trial that compared the efficacy of zanubrutinib with that of ibrutinib (Imbruvica), another FDA-approved BTK inhibitor for the treatment of patients with WM (342). Patients were divided into two groups: one group received either zanubrutinib or ibrutinib, while the other group—in which patients either had normal *MYD88* gene, which contributes to the survival of WM cells, or had a certain mutation in the *MYD88* gene—received only zanubrutinib. Approval was based on response rate and duration of response to zanubrutinib. The response rate in the first group was 77.5 percent, and 94.4 percent of the respondents had no signs of cancer 12 months after starting the treatment. The response was 50 percent in the second group. The study is ongoing and, although the initial findings are encouraging, additional data will further inform the efficacy and safety of zanubrutinib (342).

In September 2021, FDA also approved zanubrutinib for adult patients with relapsed or refractory marginal zone lymphoma (MZL)—another rare type of B-cell cancer— and who have received at least one anti-CD20-based treatment, a common treatment option for patients with cancers of B cells.

MZL is the most common type of slow-growing lymphoma and accounts for about 5-10 percent of all lymphomas (1). MZL remains largely understudied, making it challenging to define a single treatment approach for MZL patients. FDA approval of zanubrutinib for the treatment of adult MZL patients was based on findings from two clinical trials. One study included 66 MZL patients who had received at least one prior anti-CD20-based treatment, while the other study included 20 patients who had been previously treated for MZL. In the first trial, the overall response rate was 56 percent, with 20 percent of respondents achieving complete remission (343). In the second trial, the overall response rate was 80 percent, with 20 percent of respondents achieving complete remission. At the time of the approval, the duration of response at the one-year mark was estimated to be in 85 percent and 72 percent of respondents, respectively (344).

The approval of zanubrutinib for the treatment of adult MZL patients provides clinicians with additional treatment options, especially for patients in which the cancer has returned.

In December 2021, FDA expanded the use of rituximab (Rituxan) in combination with chemotherapy for pediatric patients who are between 6 months and 18 years of age; have not been previously treated; and are at an advanced stage of one of the following rare forms of B-cell cancers—diffuse large B-cell lymphoma (DLBCL); Burkitt lymphoma (BL); Burkitt-like lymphoma (BLL); or mature B-cell acute leukemia (B-AL)—that have the CD20 protein on their surface.

Rituximab was first approved by FDA in 1997 to treat non-Hodgkin lymphoma (NHL) and has become a main treatment option for a broad variety of B-cell cancers (344). Rituximab is an antibody that binds to the CD20 protein, found in abundance on the surface of cancerous B cells, and directs other immune cells to the tumor where they kill the target cancer cells, a process called antibody-dependent cell-mediated toxicity. The clinical study evaluating the efficacy and safety of the combination therapy is ongoing (346). An interim analysis of the findings was performed using data from 328 patients who were followed up for nearly 40 months. Patients receiving the combination therapy did not have detectable cancer after three years, and had an 11.6 percentage points higher survival rate (93.9 percent with combination therapy versus 82.3 percent with chemotherapy alone) (346).

Together, these approvals fulfill the unmet needs in treatment of many rare but aggressive forms of blood cancers and highlight the rapid advances spurred by the field of precision medicine (see sidebar on **Recent Advances Against Blood Cancers**, p. 83).

Combining Therapeutics to Improve Outcomes

BRAF is an enzyme with a critical role in controlling cell growth. The *BRAF* gene is changed in approximately six percent of all human cancers, including melanoma and colorectal cancer (347). Most cancer-related changes in the *BRAF* gene cause the protein to continuously stay active, thus helping cancer cells grow faster than normal cells.

One of the most common cancer-related changes in the *BRAF* gene is called BRAF V600E mutation. The BRAF V600E mutation is found in about 50 percent of melanoma patients, 10 percent of colorectal cancer patients, and 2-5 percent of non–small cell lung cancer (NSCLC) patients. Presence of BRAF V600E mutation is associated with poor outcomes for patients with certain types of cancer (347).

In June 2022, FDA approved a combination of two molecularly targeted therapeutics that inhibit activity of the BRAF protein—dabrafenib (Tafinlar) and trametinib (Mekinist)—for the treatment of adult and pediatric patients (age 6 and older) who have a solid tumor harboring the BRAF V600E mutation. The approval is specifically for patients whose cancer has either spread in the body following prior treatment or cannot be surgically removed, and who do not have any satisfactory alternative treatment options. It is important to note that the combination is not approved for patients with colorectal cancer even if the cancer carries the BRAF V600E mutation because colorectal cancer is resistant to treatment with therapeutics that inhibit the activity of BRAF.

Recent Advances Against Blood Cancers

During the 12-month period—August 1, 2021, to July 31, 2022—covered by this report, the U.S. Food and Drug Administration approved several anticancer therapeutics to treat a wide range of hematological malignancies, including the following:

MOLECULARLY TARGETED THERAPIES

Asciminib (Scemblix)

- An inhibitor of the BCR/ABL oncogene—approved in October 2021 to treat **chronic myelogenous leukemia**.

Zanubrutinib (Brukinsa)

- An inhibitor of an enzyme necessary for proliferation of B cells—approved in September 2021 to treat **Waldenström macroglobulinemia** and **marginal zone lymphoma**.

IMMUNOTHERAPIES

Brexucabtagene autoleucel (Tecartus)

- A CD19-directed chimeric antigen receptor T-cell therapeutic—approved in October 2021 to treat adult **acute lymphoblastic lymphoma**.

Ciltacabtagene autoleucel (Carvykti)

- A BCMA- directed chimeric antigen receptor T-cell therapeutic—approved in February 2022 to treat **multiple myeloma**.

Tisagenlecleucel (Kymriah)

- A CD19-directed chimeric antigen receptor T-cell therapeutic—approved in May 2022 to treat **follicular lymphoma**.

COMBINATION THERAPIES

A combination of rituximab (Rituxan)—a molecularly targeted therapeutic**—with standard-of-care chemotherapy,** approved in December 2021 to treat **diffuse large B-cell lymphoma**, **Burkitt lymphoma**, **Burkitt-like lymphoma**, or **mature B-cell acute leukemia**.

FDA approval was based on findings from three clinical trials that evaluated efficacy of the combination in adult and pediatric patients (age six and older). Patients enrolled in the studies had one of 24 different types of tumors, including cancers of skin, lung, bile duct, thyroid, brain, and gastrointestinal tract (348). A total of 41 percent of patients experienced an objective response to the treatment. The overall response rate was 46 percent for bile duct cancer, 33 to 50 percent for brain cancer depending upon how advanced the cancer was. Among pediatric patients, 25 percent experienced an overall response rate that lasted for about six months in 78 percent of patients and for about two years in 44 percent of patients (348).

The approval of the dabrafenib and trametinib combination to treat any solid tumor—with the exception of colorectal cancer—that carries the BRAF V600E mutation offers a new way to treat a wide range of patients, such as **Tyler Richards** (p. 84), who do not have other suitable treatment options. The approval also underscores the power of combining two or more targeted therapies to treat different types of cancer that share unique genetic features (see sidebar on **Advances in Precision Combination Therapy**, p. 86).

Delivering a Cytotoxic Drug Precisely to Cervical Cancer Cells

Researchers are continuously developing precise strategies that selectively target cancer cells for eradication without harming the normal tissue. Antibody-drug conjugates (ADCs), which use antibodies to deliver an attached toxin specifically to cancer cells, constitute one such strategy. The antibody used in an ADC is usually directed against a protein

Continued on page 86

Fighting Childhood Cancer with Precision Medicine

When he was just 9 months old, Tyler Richard's parents began to notice that he was not hitting the normal developmental milestones. Certain skills he had mastered, like holding a spoon or fork, slipped away. His balance declined. His parents, Ronnie and Katie Richards, worked with Tyler's pediatrician and got him into physical therapy. They took Tyler for many tests and exams that ruled out the possibility of multiple sclerosis or cerebral palsy. He was given leg braces in an effort to address his balance problems, but nothing seemed to help.

"They were putting Band-Aids on and not finding the real cause of these delays," Katie said. "So, we went ahead and ventured out of our local region and called for another neurologist. He said, 'You are correct, you need an MRI.' We went ahead and had an MRI within the month"

The scan found a tumor that was five inches by five inches and was wrapped around Tyler's cerebellum, the part of the brain that is responsible for balance, coordination, and other motor functions. Due to its location, the tumor was deemed inoperable.

"The doctors told us to go home and live every minute," Katie said.

"Knowing our path and our next steps caused me to really respect and embrace the moment," Ronnie said.

A biopsy followed by genetic testing at the University of California San Francisco found that Tyler's cancer was slow growing and had a mutation in the *BRAF* gene. Doctors advised Ronnie and Katie to wait and watch how the tumor progressed. After a year of slow growth, Tyler's tumor started to become larger, prompting Ronnie and Katie to seek treatment options.

"I was aware of chemotherapy and radiation as cancer treatments. But it was really scary for me to consider," Ronnie said.

"It was a very hard choice to make. If the tumor was going to take his life, we wanted him to live every moment. We did not want his last days to be spent in hospitals and on chemotherapy," Katie added.

It was at this time that Ronnie and Katie were given the option to enroll Tyler in a clinical trial testing a combination of dabrafenib (Tafinlar) and trametinib (Mekinist) to treat any solid tumor carrying the same BRAF mutation Tyler's tumor had. Even though Ronnie and Katie were initially apprehensive, Tyler's doctor explained the science behind this targeted treatment and why it was the best option for Tyler, and they agreed to participate.

"Science is amazing. Researchers came out with inhibitors to target his exact mutation, and we've been on the treatment now for over two and a half years with a stable tumor. It's incredible," Katie said. "Tyler has been taking his treatment morning and night. We're very grateful that it's a liquid so he can swallow it."

Katie added: "This journey is not easy. Childhood cancer is not easy, but we feel very grateful for this miracle of science."

Tyler has experienced very few issues with the treatment, other than skin rashes. Because he is receiving his treatment at home, Tyler is able to enjoy spending time with his older brother and younger sister. "Just having our family understand the situation and experience as much as we can together provides benefits for everyone," said Ronnie. "It's not easy for anyone. Everyone has their own stresses, but it helps Tyler feel embraced and comforted."

Tyler's treatment allowed him to achieve a happy milestone: kindergarten.

"I think the moment that I really saw a change in him was when he was able to attend school," Ronnie said.

"Having him graduate kindergarten and hitting a huge steppingstone in life that we didn't think he was going to hit has given us so much hope and so much excitement, and that's what we needed," Katie added.

At this time, Tyler's cancer is stable. He continues to get his clinical checkups and occasional MRIs.

"We know our life is far from normal. It is difficult for him to go to the doctor, but he does it. Our goal is Tyler's quality of life and making memories for him. We are very happy as long as he is feeling great. We feel blessed," Katie said.

Ronnie and Katie have become impassioned advocates for cancer research and finding new cures, especially for childhood cancers.

"We really hope that more research can get done and new drugs are available for children specifically, because a lot of the drugs used for childhood cancer were developed for adults," Katie said.

"As a parent, I would hope that more funding could be available to educational institutions, cancer research organizations, and cancer research foundations for research and development to occur," Ronnie said.

"I feel that more funding needs to go toward childhood cancer to find cures. We need more funding, more trials, more studies so that we can start curing these children."
Tyler's mother, Katie Richards

TYLER RICHARDS • AGE 6 • SACRAMENTO, CA

Photo © Brendan Compton

Advances in Precision Combination Therapy

According to NCI, combination therapy is a type of therapy that combines more than one method of treatment. During the 12-month period covered in this report, FDA granted approvals to combinations of molecularly targeted therapeutics and immunotherapeutics to treat multiple types of cancer. Some of these approvals are listed below:

A combination of an **immunotherapeutic**, pembrolizumab (Keytruda), and a **molecularly targeted therapeutic**, bevacizumab (Avastin), approved in October 2021, to treat **certain patients with cervical cancer**.

A combination of **two immunotherapeutics**, relatlimab and nivolumab (Opdivo) [collectively called Opdualag], approved in March 2022, to treat **certain patients with melanoma**.

A combination of **two molecularly targeted therapeutics**, dabrafenib (Tafinlar) and trametinib (Mekinist), approved in June 2022, to treat **any patient with solid tumor carrying the BRAF V600E mutation**—with the exception of colorectal cancer.

that is present in abundance on the surface of cancer cells. The choice of cytotoxic agent is informed by the cancer type as well as other pharmacological considerations, such as the effective dose of the toxin needed to kill cancer cells and the stability of the toxin inside the body. Once the antibody binds to its target on the cancer cell surface, the ADC is taken up by the cell where it releases the cytotoxic drug, which ultimately kills the cancer cell (349). This approach minimizes the side effects of the cytotoxic agent compared to a traditional systemic delivery.

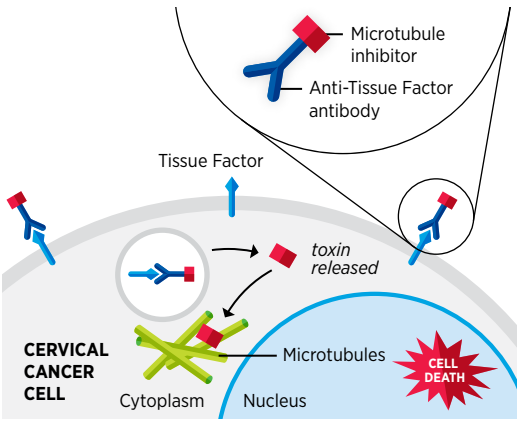
In September 2021, FDA approved tisotumab vedotin-tftv (Tivdak) for adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Tisotumab vedotin-tftv is an ADC in which an antibody directed against tissue factor—a protein that is present in abundance on the surface of cervical cancer cells and is an indicator of poor outcome (350)—is linked with a potent inhibitor of cell division. Tisotumab vedotin-tftv is the first and the only FDA-approved ADC to treat cervical cancer.

According to the 2022 estimates, more than 14,000 new cases of invasive cervical cancer will be diagnosed, and more than 4,000 women will die from cervical cancer in the U.S. (1). Although both incidence and mortality from cervical cancer have declined by greater than 50 percent since 1975 (5)—thanks to advances in prevention, early detection, and treatment—cervical cancer that returns after initial course of treatment and/or metastasizes to other organs has a very poor outcome for patients and its treatment remains a significant challenge (351).

The FDA-approval of tisotumab vedotin-tftv was based on a phase II clinical trial in which researchers evaluated the efficacy of the drug in 101 patients with recurrent or metastatic cervical cancer (352). Patients received tisotumab vedotin-tftv every three weeks unless the disease started to progress again, or the researchers considered the drug toxic for the patient. According to the study's findings, 24 percent of patients responded to the treatment, either partially (17 percent of the respondents) or completely (seven percent of the respondents) and the duration of the response was more than eight months (352).

Given the poor prognosis for patients with recurrent or metastatic cervical cancer, and the low efficacy of current therapies in treating the disease, approval of tisotumab vedotin-tftv represents a new and substantial advance for women with recurrent or metastatic cervical cancer such as **Jennifer Myers** (see p. 88).

DELIVERING CYTOTOXIC DRUGS TO CANCER CELLS



Targeting New Ways to Treat Lung Cancer

Lung cancer is the leading cause of cancer deaths—nearly 25 percent of all cancer deaths in the U.S. are due to lung cancer—making it a major public health challenge (1).

Epidermal growth factor receptor (EGFR) is an important tyrosine kinase that is present on the cell surface of many normal tissues and helps cells proliferate. Research has revealed that the *EGFR* gene acquires mutations in certain cancer types, including NSCLC (353). About 80-85 percent of lung cancers are NSCLC. Sixty percent of all NSCLCs have very high levels of EGFR on their surface and roughly 20 percent have mutations in the *EGFR* gene (1,354). Because of this knowledge, EGFR has become an important therapeutic target, and FDA has approved numerous EGFR-targeted therapies over the last two decades for treatment of NSCLC (21). However, patients eventually develop resistance to these therapies as the *EGFR* gene acquires additional alterations (see sidebar on **The Challenge of Treatment Resistance**, p. 80). For example, patients with NSCLC whose tumors harbor certain alterations, such as insertion mutations in a part of the *EGFR* gene called exon 20, do not respond well to EGFR-targeted therapeutics, such as osimertinib, and generally have poor prognosis (355).

In September 2021, FDA approved mobocertinib (Exkivity) for adult patients who have locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, and whose disease has progressed during or after chemotherapy. FDA also approved the Oncomine Dx Target Test as a companion diagnostic to select patients with EGFR exon 20 insertion mutations. Efficacy of the drug was evaluated in 114 patients who received mobocertinib daily. Overall, 28 percent of patients responded to the treatment and the response lasted more than 17 months (356). Progression-free survival was more than seven months, while the overall survival was two years (see sidebar on **Commonly Used Terms and Benchmarks in Clinical Studies**, p. 72) (356).

Mobocertinib is the first molecularly targeted drug that is directed only against EGFR for the treatment of patients with NSCLC who have EGFR exon 20 insertion mutations, and that can be taken orally.

As indicated earlier in the chapter, the *AACR Cancer Progress Reports* do not include detailed discussions of FDA approvals of anticancer therapeutics that were previously approved for a different stage of the same type of cancer. For example, during the period covered in this report, FDA approved two previously approved molecularly targeted therapeutics for treatment of early-stage breast cancer (see sidebar on **Advances Against Early-Stage Breast Cancer**, p. 90).

ADVANCES IN CANCER IMMUNOTHERAPY

Decades of research have identified ways by which the immune system detects and destroys unwanted organisms, molecules, and toxins in the human body. More recent discoveries in this area of research have allowed researchers to weaponize a patient's immune system against cancer (362), leading to the establishment of cancer immunotherapy as the most recent addition to the pillars of cancer treatment (see **Figure 8**, p. 68). Cancer immunotherapy leverages the natural ability of a patient's immune system to fight cancer using a class of drugs known as immunotherapeutics (see sidebar on **How Immunotherapeutics Work**, p. 91) (363).

Rapid advances in the development of new and improved immunotherapeutics have revolutionized cancer care of many patients. The remarkable success of these treatments in the clinic is, in part, because of the durable response in some patients with metastatic cancer. As one example, a recent study reported that the immune response in patients who had metastatic skin cancer (melanoma) and responded exceptionally well to immunotherapy lasted up to nine years following treatment (364). However, research has also found that not all patients who receive immunotherapy experience such an incredible response. Reasons for the suboptimal response to immunotherapy are many, and include the type of cancer a patient has; the stage at which the cancer is being treated; how quickly the cancer is acquiring new alterations; and how cancer cells have modified the environment around them to evade immunotherapeutics, among others (365). Furthermore, immunotherapeutics currently approved by FDA treat only a subset of cancer types (366).

Researchers are continuously investigating and developing new and improved strategies to fully realize the potential of immunotherapeutics for treating all cancers. Numerous ongoing clinical trials are evaluating a range of immunotherapeutics against new targets on cancer cells and testing the use of those we already have against additional types of cancer, alone or in combination with other types of cancer treatments (367). One major breakthrough in cancer immunotherapy is the FDA approval in March 2022 of a revolutionary immunotherapeutic, called relatlimab, in combination with nivolumab (Opdualag). Relatlimab is the first immune checkpoint inhibitor against a new target in eight years since the approval of pembrolizumab (see **Releasing the Brakes on the Immune System**, p. 90).

Another area of active research is the use of natural killer (NK) cells to develop a new class of immunotherapeutics (368,369). NK cells are a type of immune cells that rapidly kill abnormal cells by releasing cytotoxic chemicals. In several clinical studies, NK cells have proven to be safer that T cell-based immunotherapeutics for use in humans, and more effective in killing cancer cells (369). Researchers are also developing genetically modified NK cells to further enhance their ability to specifically kill cancer cells (370). Ongoing research is also focused on harnessing the ability of certain types of immune cells isolated from tumors to develop anticancer immunotherapeutics (371) (see **Looking to the Future of Cancer Science and Medicine**, p. 116).

Here, we focus on the FDA approvals of new immunotherapeutics and the expansions of the previously approved immunotherapeutics for use against additional types of cancer between August 1, 2021, and July 31, 2022 (see **Table 4**, p. 69).

Continued on page 90

Defying the Odds, Thanks to Cancer Research

In 2014, Jennifer Myers, former bank executive, went to her OB/GYN after she noticed some spotting and irregular bleeding.

"I just thought something was wrong and during the examination my doctor wanted to take a biopsy and that's how they found that I had stage I cervical cancer," Jennifer said.

Following her diagnosis, everything happened quickly.

"My doctor said, 'It's cancer, and you have an appointment in two days to meet a surgeon in Pittsburgh.' Less than a month later, I was on the operating table getting the radical hysterectomy," Jennifer continued. Following her surgery, Jennifer received internal radiation, leading to successful elimination of detectable cancer.

Three years later, in 2017, her cancer returned and was found to have spread to her pelvic wall, which excluded the possibility of another surgery.

"I was really taken off guard," she said. "I thought I did everything I was told to do the first time, and yet it came back. And I think that's when the emotions really hit me. The hardest part was going back and telling my family: my parents, my sisters, my younger nieces, and nephew."

Fortunately, she responded well to her treatment—radiation and six chemotherapy treatments over the course of seven weeks. And once again she was deemed to be in remission. However, within a year, Jennifer had a recurrence of stage IV cervical cancer that had metastasized to the lymphatic system and lung. Her oncologist told Jennifer that, with traditional treatment, she would have about 15 months to live.

A strong advocate for her own health, Jennifer was determined to get the best care possible and decided to travel to The University of Texas MD Anderson Cancer Center in Houston. After a dose of strong chemotherapy treatments that her body just couldn't withstand her OB/GYN oncologist offered her an opportunity to meet with the Targeted Therapy division which led her to a Phase I Clinical Trial. While on the experimental treatment, Jennifer's cancer was stable. After 30 months, however, the cancer stopped responding, and Jennifer exited the trial. That is when Jennifer returned to her original oncologist at MD Anderson and discussed the recently approved drug tisotumab vedotin-tftv (Tivdak).

"What attracted me to Tivdak is the fact it was just FDA approved and my oncologist really felt it was the best shot I had," she said. "And the fact that it was designed specifically for metastatic cervical cancer."

Jennifer is currently receiving infusion with tisotumab vedotin-tftv once every three weeks. She travels to Houston from her home in Pennsylvania to receive the treatment.

"Someone once said to me, 'Cancer's your new job,'" Jennifer recalled. "I truly believe that, because at some point you have to make a dedication to your treatment, especially when you're traveling out of state."

Jennifer experienced mild side effects, such as nausea, dry eyes, and fatigue, and recognizes when to rest.

"I know that there are days that it may just be me and the dogs and Netflix and a heating pad, and we're going to spend the day relaxing," she said.

The cancer diagnosis has taken a serious toll on her. "The emotional stress of thinking, 'Is this my last Christmas?' or 'Is this my last birthday with my niece?' … You always have those thoughts that go through your head."

Mental health services such as those provided by her psychiatrist at MD Anderson have helped Jennifer manage these emotional anxieties.

"I am a firm believer that as much as you pay attention to your physical health, you need to pay attention to your mental health," she said. "You really need to look at the impact that this has on you emotionally, whether it's depression, anxiety, or nervousness."

"I had a doctor once tell me, 'It's not going to do me any good to cure you physically if I ignore the mental part of it, where you can't even get out of bed because you're so depressed,'" she added.

Jennifer stressed the importance of having a support network that includes mental health professionals, social media support groups, and caregivers like her husband in supporting her mental health.

"They live it every second. They live the diagnosis. They're sitting with you when doctors say, 'Your wife has cancer,'" she reflected.

So far, Jennifer is doing well, and her cancer continues to respond to treatments. She credits the remarkable success in her battle with cancer to the basic research studies performed by scientists and clinicians. She wants cancer researchers, physician-scientists, oncologists, nurses, and others working in cancer medicine to understand that what they do has a meaningful impact on real people.

"I wouldn't be here today if it wasn't for the people that developed new drugs or performed clinical trials," she said. "The people who work day in and day out in the cancer field. They are the real superheroes of the world."

And those superheroes have enabled her to keep going.

"I don't know how my story will end, but in no chapter will it say that I ever gave up."

"I was given 15 months in November of 2018, and I would have never guessed that I'd be sitting here in 2022."

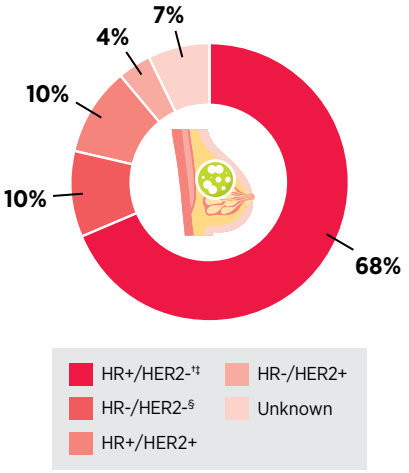
JENNIFER MYERS • AGE 51 • INDIANA, PA

Photo © Jack Wrenn

Advances Against Early-Stage Breast Cancer

Breast cancer is categorized into distinct subtypes based on the presence or absence of three proteins—estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (357).

PERCENT OF FEMALE BREAST CANCER CASES BY CANCER SUBTYPE*



* Data Timeframe: 2015-2019; Source: (358)

† HR refers to hormone receptors and includes both ER and PR

‡ (+) and (-) signs indicate presence or absence, respectively, of the indicated protein

§ Breast cancers that are negative for HR and HER2 are also called triple negative breast cancers or TNBC.

Although there are several FDA-approved targeted therapies to treat breast cancer that have higher than normal levels of HER2 protein (HER2+), these therapies are less effective against breast cancers that have reduced levels of HER2 protein or have completely lost the protein (HER2-) and HER2- early-stage breast cancer has been particularly challenging to treat (359). However now there are some options to treat HER2- early-stage breast cancer:

ABEMACICLIB (VERZENIO)

FDA APPROVED

OCTOBER 2021

Approved to treat patients who have HER- early-stage breast cancer and a high likelihood of cancer recurrence. Abemaciclib is an inhibitor of CDK4/6 proteins that are essential for cells to divide (360).

OLAPARIB (LYNPARZA)

FDA APPROVED

MARCH 2022

Approved to treat patients with high-risk early-stage breast cancer, who have a harmful or suspected harmful inherited mutation in the *BRCA* gene. Olaparib is an inhibitor of an enzyme called poly (ADP-ribose) polymerase, which is crucial for repairing the damaged DNA (361).

Releasing the Brakes on the Immune System

Breakthrough discoveries over the past few decades have revealed that T cells, a type of immune cell, are naturally capable of destroying cancer cells. Research has also revealed that some tumor cells "learn" to avoid destruction by T cells. One of the ways by which tumor cells do so is by increasing levels of certain proteins on their surface that attach to and activate "brakes" on T cells, thus stopping them from attacking cancers. These brakes are proteins on the surface of T cells and are called immune checkpoint (IC) proteins.

Researchers have identified many IC proteins and their binding partners on tumor cells, four of which—CTLA-4, PD-1, and PD-L1, and most recently, LAG-3—have proven to be effective targets for therapeutic intervention (see **Figure 11**, p. 94). This knowledge has led to the development of a new class of therapeutics—called immune checkpoint inhibitors (ICIs)—that can release the brakes on T cells and trigger T cells to destroy cancer cells (372).

One of the major advantages of ICIs is their effectiveness against different types of cancer, as highlighted by FDA approvals of ICIs to treat multiple types of cancer (see **Figure 12**, p. 95). During the 12-month period covered in this report, the FDA approved relatlimab (Opdualag), which binds to and releases a brake called LAG-3 on T cells, in combination with an already approved ICI, nivolumab (Opdivo), to treat metastatic melanoma. As of July 31, 2022, one or more ICIs have been approved for treating 18 types of cancer and for treating any types of solid tumors that are characterized by certain molecular features, such as microsatellite instability (MSI)–high, DNA mismatch–repair deficiency (dMMR), and tumor mutational burden (TMB)–high.

In March 2022, FDA approved a combination of two ICIs, nivolumab and relatlimab. The combination is approved to treat adult and pediatric (≥12 years old) patients with previously untreated melanoma whose cancer has either spread to other organs or cannot be removed by surgery.

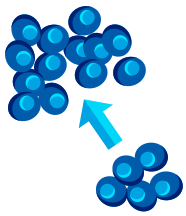
Deaths related to invasive melanoma have declined sharply at a rate of four percent every year from 2014 to 2019—the most recent data year—thanks to breakthroughs in treatment of the cancer (1,21). However, treatment of melanoma that has spread to other parts of the body or cannot be surgically removed remains a significant challenge. The approval of relatlimab is a major advance as it is the first FDA-approved drug to block the activity of LAG-3, a protein

How Immunotherapeutics Work

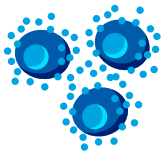
Immunotherapeutics utilize multiple mechanisms to unleash a patient's immune system against cancer:

Some **release the brakes** on the natural cancer-fighting power of the immune system, for example, relatlimab (Opdualag), the newest and the ninth member of this class of immunotherapeutics approved in March 2022 (see **Releasing the Brakes on the Immune System**, p. 90).

Some **provide more cancer-targeted immune cells** called T cells to amplify the killing power of the immune system, for example, the chimeric antigen receptor T cell therapeutic, brexucabtagene autoleucel (Tecartus), approved in October 2021 to treat acute lymphoblastic lymphoma in adults.



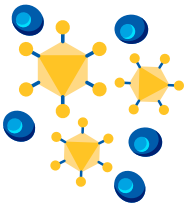
Some **enhance T-cell function** to increase the killing power of the immune system, for example, interleukin-2 (Aldesleukin).



Some **trigger cancer-fighting T cells** to enhance the killing power of the immune system; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).

Some **flag cancer cells for destruction** by the immune system, for example tebentafusp-tebn (Kimmtrak), which was approved by FDA in January 2022 to treat a rare type of eye cancer.

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).



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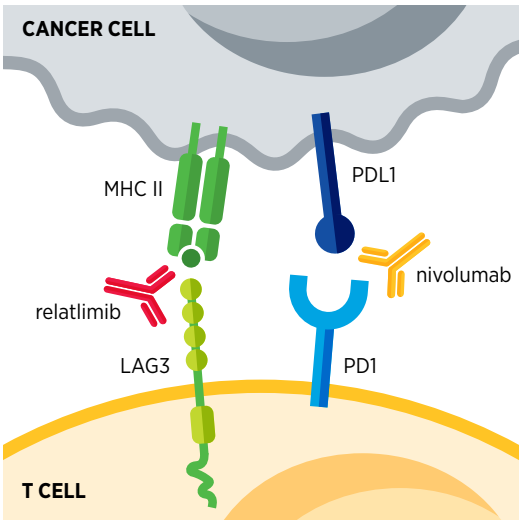
THE FIRST IMMUNE CHECKPOINT INHIBITOR TARGETING LAG-3



on the surface of T cells that also functions as a brake similar to CTLA-4 and PD-1. It is also the first FDA-approved ICI against a new immune checkpoint in more than eight years. Importantly, the approval brings hope for patients, such as **Johnny Borgstrom** (p. 92), who had limited options for treating an otherwise difficult-to-treat type of skin cancer.

FDA approval was based on a phase II/III clinical study that compared efficacy of the relatlimab and nivolumab combination with nivolumab alone—which is the standard-of-care—in patients with previously untreated melanoma whose cancer had spread within the body or could not be removed surgically (373). A total of 714 patients were randomly selected to receive the combination of nivolumab and relatlimab or nivolumab alone. Compared to patients who received nivolumab alone, patients who received the drug combination had longer progression-free survival (4.6 months versus 10.1 months, respectively) (373).

It is important to note that the relatlimab and nivolumab combination appears to be associated with fewer side effects than another combination of ICIs, also approved for the treatment

Continued on page 94

Overcoming Stage IV Melanoma, Thanks to a Clinical Trial

In October 2017, Johnny Borgstrom of Big Cabin, Oklahoma, noticed a bump on his head. He mentioned it to his primary care doctor, who set up an appointment with a dermatologist for February.

By November, the bump had grown to the size of a nickel. The next month, the bump was the size of a quarter and had started to bleed. That's when Johnny's daughter, who works for an urgent care provider, got a colleague to help find a dermatologist who could see him soon.

A biopsy revealed that Johnny had an aggressive form of melanoma, and the dermatologist sent him to a surgeon in Tulsa–nearly 60 miles away.

"I have no history of cancer in my family. I was shocked. It was devastating," recalled Johnny, now 70, who retired from the United Parcel Service after 36 years.

Over the next three months, from January to March 2018, he had three surgeries, including one that revealed that the melanoma had spread to his lymph nodes. A follow-up exam found that the cancer had spread to Johnny's lungs.

That's when Johnny decided he wanted a second opinion. His daughter suggested The University of Texas MD Anderson Cancer Center in Houston.

"I thought for a second, because that was a 12-hour drive. I really did not want to drive that far. But eventually I decided to go to MD Anderson. So that was the start of my journey," Johnny said.

A lung biopsy confirmed that Johnny had stage IV melanoma. His oncologist, Hussein A. Tawbi, MD, PhD, mentioned a clinical trial testing a therapeutic combining the immune checkpoint inhibitors, nivolumab and relatlimab-rmbw, for melanoma and asked if he would be willing to participate.

"People don't live very long with the stage of cancer I had," Johnny said, "So I told him, 'Let us do it if it would save another child's or adult's life, even if I did not make it.'"

In June 2018, six months after his initial diagnosis, Johnny started receiving the investigational treatment, which involved an infusion every 28 days. Each time, he and his family had to travel to Houston for the treatment.

"I thought to myself that we're going to be positive," Johnny recalled. "Every time we were in Houston, we did something fun. We made our 12-hour-long trip a positive family affair," Johnny said.

Johnny had a great experience with his cancer care team.

"The nurses and the doctors were part of my family, and we were part of their family. It was just an unbelievably great experience," Johnny said.

Those relationships with his care team were key, especially during COVID-19, when Johnny's family couldn't accompany him into the hospital for treatments.

"My family members had been my supporters throughout, even when they were not with me. Back home, I had people praying for me. God was with me all the way through, and arranged for all of this, the doctors, the medicine, everything. It was just like another treatment. I had no fear," he said.

Johnny's cancer was responding well to his treatment. In June 2019, the cancer had disappeared completely. Even though Dr. Tawbi was comfortable taking Johnny off the clinical trial, Johnny decided to continue participating in the study. His last treatment was in May 2020.

During the course of his treatment, Johnny experienced some side effects related to his heart, thyroid, and eyes, but his cancer care team had prepared him well in advance and was readily available for assistance when he needed it.

"My doctors were amazing. Dr. Tawbi explained to me everything that could happen because of the treatment. So, it was not a surprise to me," he said. "My quality of life is great."

And he has been cancer free since May 2020.

Johnny's positive experience and outcome from participating in the clinical trial has made him an enthusiastic advocate for clinical research.

"I have lost close friends to cancer. I tell anyone who has cancer: 'Don't be afraid of a trial. Go for it. Doctors take the greatest care of you. You are not alone,'" Johnny said.

Johnny continued with a message for cancer researchers, adding: "Keep doing what you are doing. Keep looking for new medicines to cure cancer. Keep up the good work."

He added that policy makers need to robustly fund cancer research. "Researchers need the funding to find new treatments for cancer," he said.

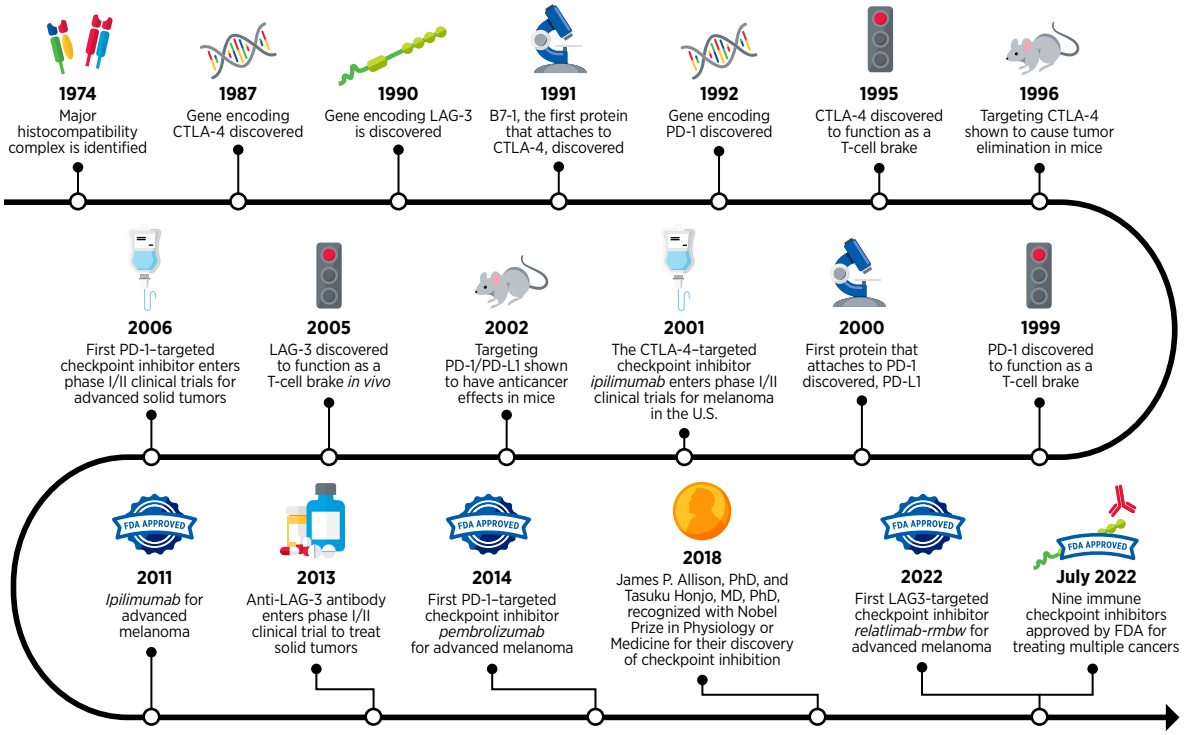
"Don't be afraid of a trial. Go for it. Doctors take the greatest care of you. You are not alone."

JOHNNY BORGSTROM • AGE 70 • BIG CABIN, OK

Photo © Mark Weiss

FIGURE 11

Decades of Breakthroughs Along the Way to Developing Immune Checkpoint Inhibitors



Immune checkpoint inhibitors (ICIs) are cancer immunotherapeutics that work by releasing "brakes" called immune checkpoint (IC) proteins on the surface of cancer-fighting immune cells called T cells. Decades of rapid advances in basic and clinical research led to the approval of the first ICI, ipilimumab (Yervoy), by the U.S. Food and Drug Administration (FDA) in March 2011. Ipilimumab targets an IC protein on T cells called CTLA-4. Several other ICIs target a second immune checkpoint protein called PD-1. The first of these immunotherapeutics approved by FDA was pembrolizumab (Keytruda) in September 2014, and dostarlimab-gxly—the newest member of this class of immunotherapeutics—was approved in April 2021. In March 2022, FDA approved a new ICI targeting a different IC protein, LAG-3. Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4, PD-1, and LAG-3, identification of the proteins that attach to and trigger the brake function of CTLA-4, PD-1, and LAG-3, and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered.

of melanoma—nivolumab and ipilimumab. Less than 20 percent of patients who received the relatlimab and nivolumab combination reported serious side effects compared to nearly 60 percent of patients who received the nivolumab and ipilimumab combination (374).

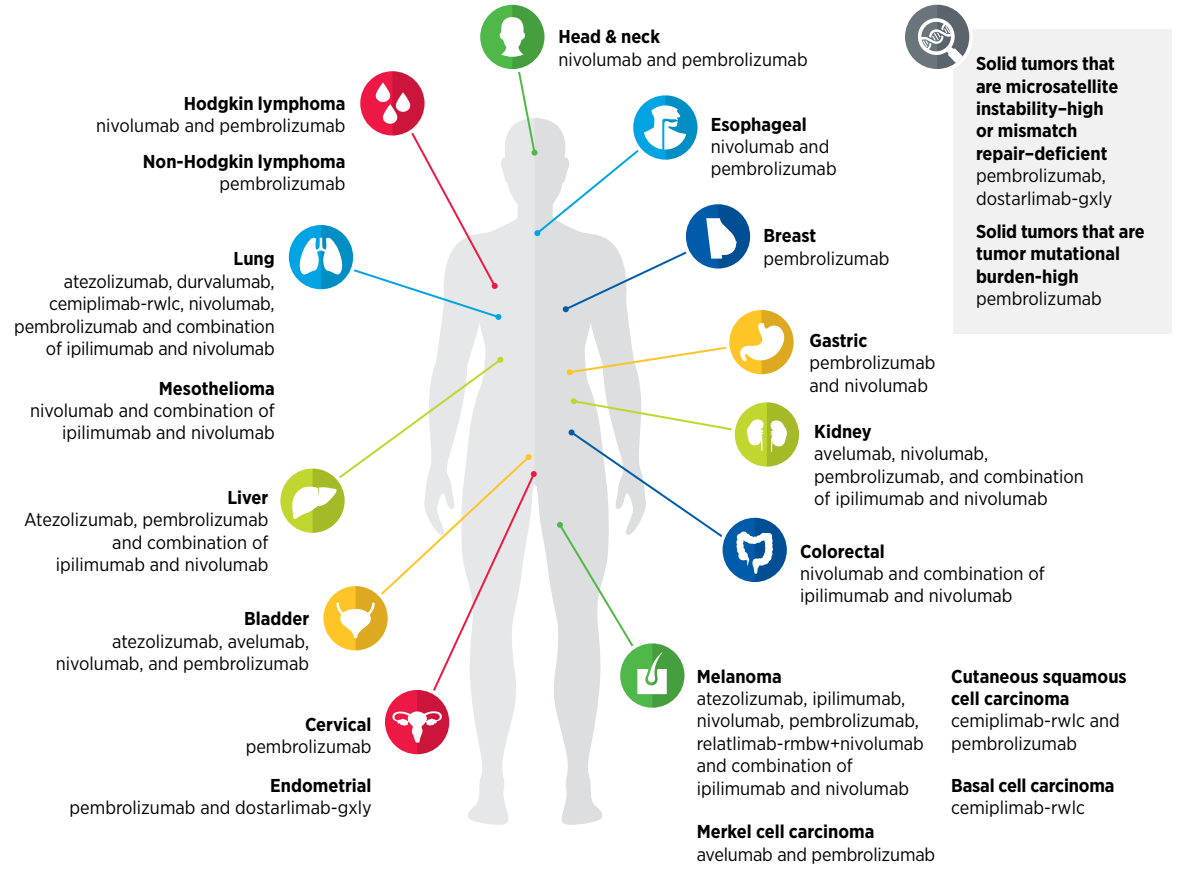
Although the study is ongoing, approval of relatlimab marks a significant advance in the field of ICIs, and provides more treatment options for patients who have advanced, and particularly harder to treat, cancer.

In August 2021, FDA approved dostarlimab-gxly (Jemperli) for adult patients who have no satisfactory alternative treatment options for their advanced stage or returning solid tumors that are dMMR, a specific genetic feature of many types of cancer. FDA also approved the VENTANA MMR RxDx Panel as a companion diagnostic to select patients with dMMR solid tumors for treatment with dostarlimab-gxly.

FDA approval of dostarlimab-gxly, which was first approved in April 2021 to treat advanced endometrial cancer with dMMR (21),

FIGURE 12

The Expanding Utility of Immune Checkpoint Inhibitors

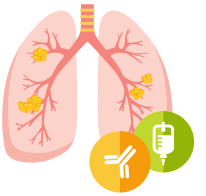


In March 2011, FDA approved the first immune checkpoint inhibitor (ICI), ipilimumab (Yervoy), for metastatic melanoma. Nearly four years later, a second ICI, pembrolizumab (Keytruda), was approved, also for metastatic melanoma. Since then, another seven ICIs have been approved by FDA and include: atezolizumab (Tecentriq), avelumab (Bavencio), cemiplimab-rwlc (Libtayo), dostarlimab-gxly (Jemperli), durvalumab (Imfinzi), nivolumab (Opdivo), and the anti-LAG-3 antibody relatlimab in combination with nivolumab (Opdualag). In addition, FDA has expanded the number of cancer types for which there is at least one ICI approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of July 31, 2022, one or more checkpoint inhibitors were approved for treating 18 types of cancer and for treating any type of solid tumor characterized by the presence of certain molecular characteristics, including microsatellite instability–high, DNA mismatch–repair deficiency, and tumor mutational burden–high. In addition, with all the ICIs approved for treating multiple types of cancer, there are several cancer types for which there is a great selection of ICIs available as treatment options.

Adapted from (21).

to treat any solid tumor with dMMR was based on clinical trials that evaluated the efficacy of the immunotherapeutic. Overall, 41.6 percent of patients responded to the treatment. The median duration of the response was nearly three years, with more than 95 percent of the respondents responding for at least six months (376). The approval adds dostarlimab-gxly to a growing list of targeted therapeutics being used in the clinic to treat different types of cancer that share similar genetic feature(s).

In patients who have a certain type of early stage lung cancer, **treatment with chemotherapy and nivolumab** before surgery **increased the proportion of patients with no signs of cancer in the tissue removed during surgery 11 times**, compared to those treated with chemotherapy and placebo (375). FDA approved the treatment in March 2022.



In addition to the remarkable benefit of ICIs in saving and improving lives of patients across a broad spectrum of cancer types, studies are highlighting the potential utility of ICIs beyond cancer treatment. For example, findings of a recent study indicate that pembrolizumab can increase viral production from dormant HIV-infected cells, which are usually undetected by the host immune system and are unresponsive to ART. By increasing HIV viral production in these latently infected cells, pembrolizumab could facilitate immune recognition and reduce the number of HIV-infected cells that persist after ART, potentially aiding in curing HIV in addition to treating cancer (378). Additional studies will help determine whether this observation may translate into cures for patients with HIV and cancer, and whether pembrolizumab and other ICIs have similar additional benefits beyond cancer.

It should be noted that realizing the full potential of ICIs in treating cancers is somewhat restricted by the fact that not all types of tumors respond to these immunotherapeutics and many that do eventually develop resistance to the treatment. Researchers are continuously working to develop innovative and improved strategies to bring the promise of these immunotherapeutics to as many additional cancer patients as possible. It will also be important to evaluate and address the short- and long-term side effects and late effects arising in patients who are treated with these newly approved immunotherapeutics (see sidebar on **Common Side Effects of Immune Checkpoint Inhibitor**, p. 104).

Boosting the Killing Power of the Immune System

T cells are specialized to destroy unwanted microbes, such as infectious pathogens, or cells, such as a cancer cell, in the body. However, T cells only go on the attack after a specialized immune cell has "presented" them with a piece of the microbe or cancer cell that is present in the body (see sidebar on **Key Cells in the Immune System**, p. 26). Researchers have leveraged this knowledge to develop a new class of immunotherapeutics, called bispecific antibodies, which bypasses the intermediate step and directly brings the tumor cell and T cell together. Ongoing research is focused on developing safe and effective variations of these immunotherapeutics that can flag cancer cells so that the immune system can destroy them (379).

In a small phase II clinical trial, all 12 patients with dMMR rectal cancer who were **treated with dostarlimab-gxly** showed a **complete remission of the disease**, and have been cancer free two years after the treatment (377).

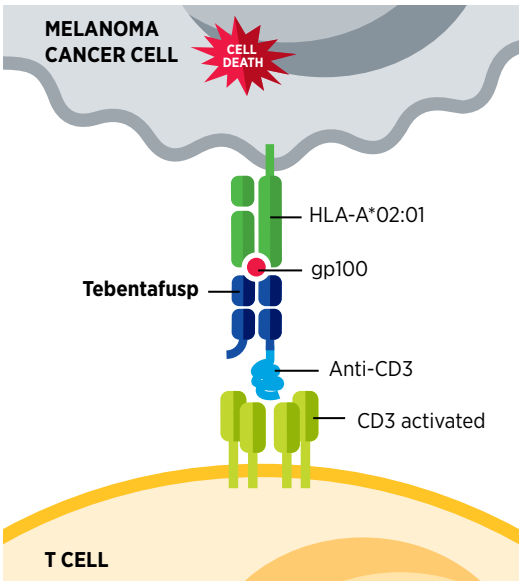
Uveal melanoma, also called ocular melanoma, is a cancer that forms in the middle layer of the wall of the eye. Although rare, this type of cancer is often fatal once it spreads to other parts of the body, which happens in about half of all cases. There was no standard treatment for metastatic uveal melanoma until recently (380).

In January 2022, FDA approved tebentafusp-tebn (Kimmtrak) for treatment of certain patients with metastatic uveal melanoma whose cancer cannot be surgically removed or has spread to other organs in the body. The approval is for adult patients whose cells have a marker on their surface called human leukocyte antigen (HLA)-A*02:01, which is a protein present in about half of all White people, the population most affected by the disease. Tebentafusp-tebn is only the second bispecific T-cell engager approved by FDA and is the first and only treatment for patients with metastatic uveal melanoma.

Tebentafusp-tebn is a bispecific antibody, which means that it can recognize two different types of molecules simultaneously. One end of tebentafusp-tebn binds to a protein, called gp100, which is present in abundance on the surface of melanoma cells (381). The other end binds to the protein CD3 on T cells, bringing them in close proximity to the melanoma cells, where the immune cells can attack and destroy the cancer cells. For tebentafusp-tebn to recognize and bind to gp100-expressing melanoma cells, these cells must also express HLA-A*02:01 (382).

The approval was based on a phase III clinical trial, in which 378 patients were randomly assigned to either the tebentafusp-tebn group (252 patients) or the control group (126 patients) (383). The control group received one of the three established therapies—pembrolizumab, ipilimumab, or dacarbazine. At the one-year follow-up, the overall survival was 73 percent in the tebentafusp-tebn group and 59 percent in the control group. Treatment with tebentafusp-tebn increased survival without any progression of the disease by 63 percent (31 percent in the tebentafusp-tebn group versus 19 percent in the control group at six months). Furthermore, nine percent of the patients in the tebentafusp-tebn group had their tumors shrink in response to treatment compared to five percent in the control group (383).

HOW DOES TEBENTAFUSP-TEBN RECOGNIZE MELANOMA CELLS?



Engineering Immune Cells to Eliminate Cancer

Adoptive cell therapy (ACT), also called cellular immunotherapy, is designed to dramatically increase the number of cancer-killing T cells, thus giving a patient's immune system a boost to seek and destroy cancer cells (384) (see sidebar on **What Is Adoptive T-Cell Therapy?**, p. 98).

ACT is one of the more recent immunotherapeutic approaches that have revolutionized the treatment of certain types of blood cancer and transformed the lives of many adult and pediatric patients (385). However, treating patients with ACT, such as with one of the FDA-approved CAR T-cell therapies, is a complex procedure that can only be performed at specially certified health care facilities by highly trained medical professionals (see sidebar on **What Is Adoptive T-Cell Therapy?**, p. 98). Furthermore, some of the side effects of CAR T-cell therapies can be potentially life threatening, such as the cytokine release syndrome in which the patient's immune system overreacts by rapidly releasing certain types of molecules into the blood. CAR T-cell therapies have also proven less successful against solid tumors (386). Developing simpler and safer ways to bring the promise of this class of immunotherapeutics to patients is an area of active research. One exciting approach under investigation is to combine the power of cancer immunotherapy with the potential of stem cells that can be genetically engineered to make "designer" immune cells with enhanced antitumor activity (387).

The potential of ACT for the effective treatment of several types of blood cancer is underscored by the FDA approvals of the new uses of previously approved CAR T-cell therapies.

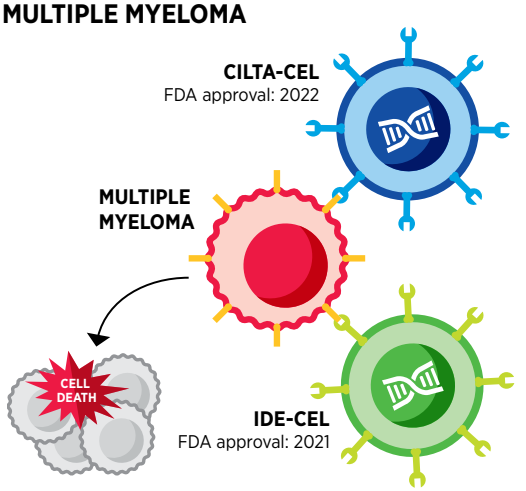
During the 12 months covered in this report, FDA approved ciltacabtagene autoleucel (Carvykti) to treat multiple myeloma; brexucabtagene autoleucel (Tecartus) to treat acute lymphoblastic leukemia in adults; and tisagenlecleucel (Kymriah) to treat follicular lymphoma.

Multiple myeloma remains one of the most diagnosed blood cancers in the U.S. (1). Despite the advances in recent years against the disease (21), many patients eventually develop resistance to treatment over time and then the disease progresses. In February 2022, FDA approved ciltacabtagene autoleucel (also called cilta-cel) for the treatment of adults with myeloma whose cancer has returned or does not respond to treatment after four or more prior lines of lines of treatments.

Cilta-cel is directed against the protein B-cell maturation antigen (BCMA) on cancer cells. Expression of BCMA is largely restricted to plasma cells, which are blood cells that make antibodies to protect against infections (388), and is much higher in myeloma cells compared to normal plasma cells (389). Cilta-cel approval was based on results from a phase I/II clinical trial. Study participants received a single infusion of cilta-cel and 98 percent of them responded completely or partially to the treatment. Importantly, there were no signs of the cancer in the bone marrow or blood for 77 percent of participants a year after infusion and the overall survival rate was 89 percent (390). Approval of cilta-cel marks the second CAR T-cell therapy option for patients with advanced multiple myeloma; in April 2021, FDA approved idecabtagene vicleucel or ide-cel (Abecma), the first ever CAR T-cell therapy to treat multiple myeloma (21).

Acute lymphoblastic leukemia (ALL) is a cancer of lymphoblasts, a type of blood cells that eventually develop into the immune system. ALL progresses rapidly and requires immediate treatment. Although most cases of ALL occur in children, about 80 percent of ALL deaths occur in adults (1). Adults with ALL

THE TWO FDA-APPROVED CAR T-CELL THERAPIES FOR TREATING MULTIPLE MYELOMA

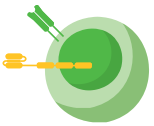


What Is Adoptive T-Cell Therapy?

Adoptive T-cell therapy (ACT), also called cellular immunotherapy, dramatically increases the number of cancer-killing 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 or genetically enhanced T cells are then reinfused in the patient to help eliminate cancer cells.

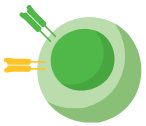
TYPES OF ACT

Currently, there are three types of adoptive T-cell therapies:



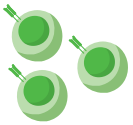
Chimeric antigen receptor (CAR) T-cell therapy

T cells are harvested from a patient's blood and genetically modified in the laboratory to have a new engineered gene that makes a protein called a CAR, which comprises parts of several different proteins and is designed to bind a specific surface protein on patient's cancer cells. The genetically enhanced T cells are expanded in number and infused back into the patient. The CAR modification helps the T cells directly bind to and attack the patient's cancer cells.



T-cell receptor (TCR) T-cell therapy

T cells are harvested from a patient's blood and genetically modified in the laboratory to have a new gene that makes a protein called a TCR, which recognizes a small fragment of a protein on the surface of patient's cancer cells. The genetically enhanced T cells are expanded in number and infused back into the patient. The TCR modification helps the T cells seek out patient's cancer cells more effectively and triggers them to attack the patient's cancer cells.



Tumor-infiltrating lymphocyte (TIL) therapy

T cells are harvested directly from a patient's tumor, expanded in number in the laboratory, and infused back into the patient. Many of these T cells naturally recognize and kill the patient's cancer cells.

ACT APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION (FDA)

As of July 31, 2022, there are six distinct FDA-approved CAR T-cell therapies—the only type of ACT approved so far—to treat different cancer types:

- **Axicabtagene ciloleucel (Yescarta)**
  First approved in 2017, to treat adult patients with certain types of B-cell lymphoma, such as **Alex Gonzalez Franco** (see p. 100).
- **Brexucabtagene autoleucel (Tecartus)**
  First approved in 2020, to treat patients with relapsed or refractory mantle cell lymphoma.
- **Ciltacabtagene autoleucel (Carvykti)**
  First approved in 2022, to treat adult patients with relapsed or refractory multiple myeloma.
- **Idecabtagene vicleucel (Abecma)**
  First approved in 2021, to treat adult patients with relapsed or refractory multiple myeloma.
- **Lisocabtagene maraleucel (Breyanzi)**
  First approved in 2021, to treat adult patients with certain types of B-cell lymphoma.
- **Tisagenlecleucel (Kymriah)**
  First approved in 2017, to treat adults with certain types of B-cell lymphoma and young adult patients up to age 25 with certain types of lymphoblastic leukemia.

either do not respond at all to the available treatments or those who do respond usually have their cancer return (391). These patients have a renewed hope with the approval of the first CAR T-cell therapy for the treatment of adult ALL.

In October 2021, FDA approved brexucabtagene autoleucel (Tecartus) for adult patients with B-cell precursor acute lymphoblastic leukemia (ALL) that has either returned after initial treatment or does not respond to the treatment. The approval was based on a phase I/II clinical study in which 55

patients received a single infusion of the drug (392). Overall, 71 percent of the patients had complete remission with or without their white blood cell count returning to normal at median follow-up of 16 months. The 58 percent of patients who had complete remission had no signs of cancer after more than a year of receiving the treatment, and more than half of all respondents were alive nearly two years after the treatment (392). This is remarkable news for adult patients with ALL who, even when responding to other available immunotherapies, such as blinatumomab (Blincyto), often have their cancer return.

Follicular lymphoma (FL) is a form of B-cell NHL, which is the most common type of lymphoma (1). Although FL responds well to initial treatments, it remains difficult to cure because many patients develop resistance to the treatment (393). In May 2022, FDA approved tisagenlecleucel for adult patients with FL whose cancer has returned or become resistant after two or more lines of systemic therapy. Findings of a phase II clinical trial, involving more than 90 patients, led to the FDA approval. Overall, 86 percent of patients responded to the immunotherapeutic, and 69 percent responded completely. Importantly, 75 percent of the respondents were still in response at the nine-month follow-up (394).

Sharing Experience with Lymphoma and CAR T-Cell Therapy to Help Others Make Informed Decisions

In October 2021, Alex Gonzalez went to an urgent care facility, seeking relief for severe abdominal pain. The medication that he was prescribed didn't alleviate the discomfort and he decided to follow up with his primary care physician.

Alex received a call from her the day after his visit.

"She asked, 'How far are you from the emergency room?' I asked her why and she responded, 'Because you have a life-threatening situation. I need you to go to the emergency room right now,'" Alex said.

Alex was at work at the time, even though he was still in pain. But after speaking with his doctor, he went home, talked with his wife, and headed to the hospital.

At the hospital emergency room, the doctors ran a series of tests. At this point, Alex had no idea what was going on.

"I thought it was something related to my gastrointestinal pain. Maybe I was eating too much, or I was sitting oddly for long hours," Alex said.

After Alex waited for about three hours in the ER, a doctor told him that he suspected Alex had lymphoma. "I didn't know what lymphoma was, exactly. I knew it was a type of cancer," Alex said. A million questions ran through his head.

Alex met with an oncologist the following morning. She informed him that, based on his scans, it was most likely that Alex had lymphoma, but that he needed a biopsy to confirm the diagnosis. Alex decided to get a second opinion, and after another series of tests and a biopsy, he was diagnosed with transformed large B-cell lymphoma, the most common form of non-Hodgkin lymphoma.

Alex was initially treated with chemotherapy in November 2021. He continued with this treatment up until March 2022.

That's when his cancer stopped responding. Alex and his wife, Raquel Castellanos, began researching other therapeutic options, including a form of immunotherapy known as CAR T-cell therapy. On April 1, 2022, the FDA approved axicabtagene ciloleucel (Yescarta) as a second-line therapy for Alex's form of lymphoma.

This seemed like a promising option, but as Alex and Raquel debated whether to try the treatment, they discovered that there was no information on how Hispanic patients like Alex had fared with the treatment. Being a cancer researcher herself, Raquel understood data from one specific racial or ethnic group can't always be extrapolated to other populations.

"When you have cancer, decisions are very important. You don't have a month or six months to decide. You need information to make the right decisions, and if that information is available because someone else underwent that experience, that's going to help a lot of people," said Alex.

Despite their concerns, Alex decided to proceed with the CAR T-cell therapy, believing that it was the best available option. Alex received the infusion of CAR T cells in May 2022.

"We read a lot about the side effects. So, we knew in advance about the chills, the nausea, and the fevers," Alex recalled. "The same day I received the CAR T cells, I was vomiting. I was with some pain and the next day I was with a high fever going up to 105 degrees for three days," Alex said.

Alex's memory of the days that ensued is hazy at best.

"That part of my memory was erased. It is very hard to explain; it's hard for you to be in a situation when you don't know what is happening with you," he said. "They were asking me questions every day, about my name, what I was doing in that hospital. And sometimes you don't remember."

Alex's health has improved steadily.

"I have my strength coming back little by little. Based on the reports, my immune system is getting better. I think that I am feeling better every day," Alex said.

His health care providers are monitoring his recovery remotely, a practice that is increasingly becoming part of routine cancer care. A nurse comes to his home once a week to check on his vitals, while Alex must do that by himself every day. All his health information is collected through a mobile device and is sent to his health care team each day.

"The follow-ups are day by day. If something concerning happens, the doctors can see it and they call me right away, just to double check or to ask me questions about how I'm feeling," Alex said.

Alex hopes that by sharing his story, he can raise awareness among his friends and family of the importance of regular health checkups.

"It's better to do health checkups on time. Because sometimes we forget, and we put ourselves last," Alex said.

He also hopes that by sharing his experiences with cancer and the lessons he has learned along the way, he can help other patients. He also hopes that other Hispanic patients can look to his story to make timely and informed decisions about their cancer care.

"It's better to do health checkups on time. Because sometimes we forget, and we put ourselves last."

ALEXANDER (ALEX) GONZALEZ FRANCO • AGE 52 • NORRISTOWN, PA

Photo © Nor Idoksal

Supporting Cancer Patients and Survivors

IN THIS SECTION YOU WILL LEARN:

- As of January 2022, there are more than 18 million cancer survivors in the United States with 67 percent age 65 or older. The number of survivors is expected to grow to 26 million by 2040 with 74 percent expected to be 65 or older.
- Survivors of cancer face unique challenges associated with their diagnosis. These challenges can continue after completion of treatment and include side effects from medications, financial toxicity, reduced health-related quality of life, increased risk of new primary cancers, and increased psychosocial challenges.
- Exercise, a healthy diet, and smoking cessation are all ways to improve the survivorship experience.
- Successful survivorship relies on the use of patient navigators to coordinate cancer care, support for family caregivers, and equitable access to telehealth.

According to NCI, a person is considered a cancer survivor from the time of cancer diagnosis through the balance of his or her life. Each person diagnosed with cancer has a unique experience ranging from successful treatment and living cancer free for the remainder of life; to experiencing varying degrees of side effects; and/or experiencing a subsequent cancer diagnosis with the same or a different type of cancer.

Advances in treatments through dedicated efforts of researchers across the health care spectrum have led to more survivors living longer and fuller lives after a cancer diagnosis. As of 2022, more than five percent of the U.S. population is living with a history of a cancer diagnosis, equating to more than 18 million people (2); three out of four U.S. families have at least one member who has experienced a cancer diagnosis (395). This is in stark contrast to 50 years ago, when cancer survivors constituted only 1.4 percent of the U.S. population. By 2040, there are expected to be 26 million survivors in the U.S. population (2), necessitating increased understanding of their challenges, how to improve the quality of their lives, and how to make sure their care is accessible and equitable.

In recent years, there has been a growing appreciation of the impact of a cancer diagnosis on friends, family, and caregivers, necessitating increased focus on the need to support patients along with their support structure to improve the survivorship experience.

The following section highlights the challenges faced by cancer survivors and their caregivers with a special emphasis on adolescents and young adults (AYAs), older adults, and the medically underserved. Later sections identify progress that has been made in improving the survivorship experience.

Challenges Faced by Cancer Survivors

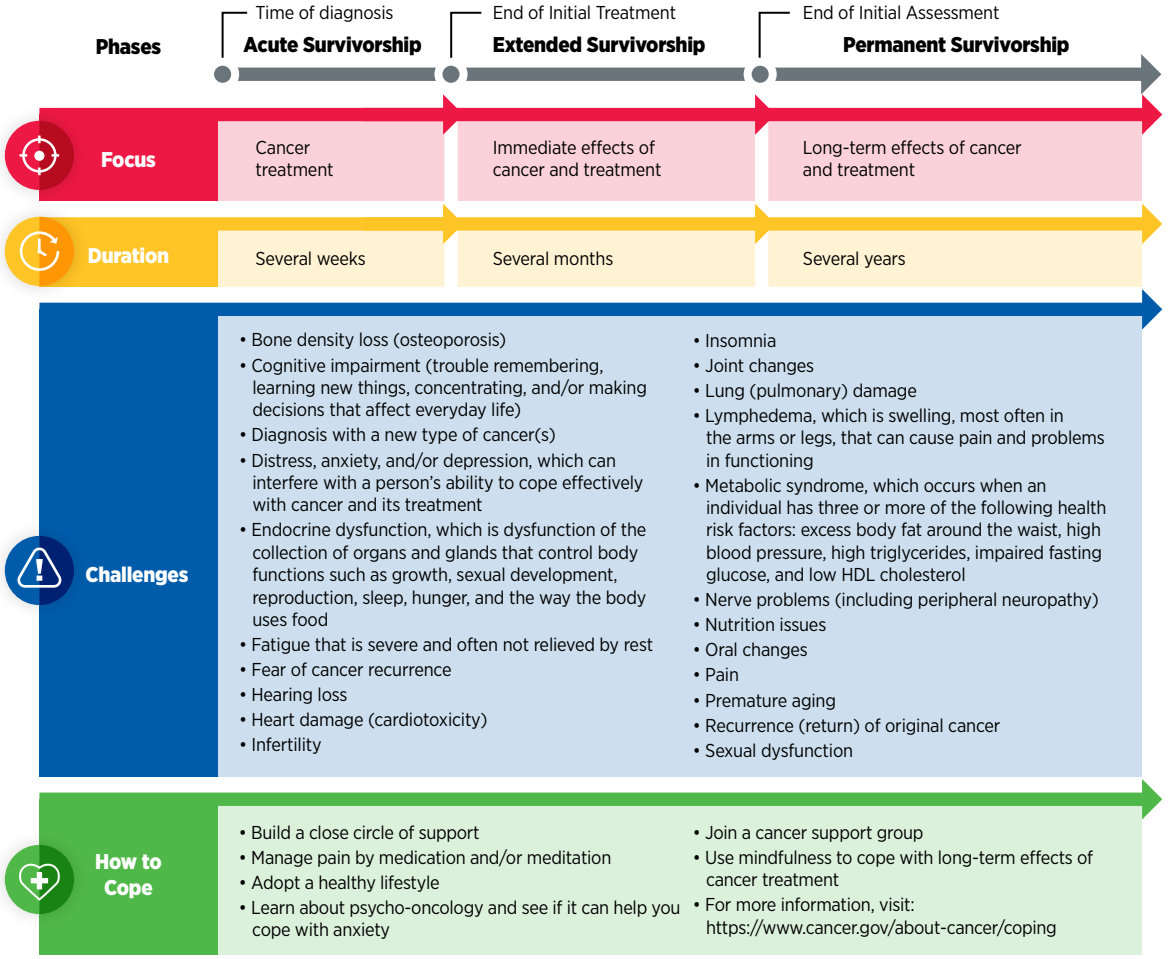
Cancer survivors often face physical, psychosocial, and financial challenges that are attributable to the cancer itself and the treatments. Furthermore, a survivor's support network including friends, family, and caregivers also experiences challenges related to caring for the survivor. Although research is ongoing, a greater understanding of these challenges and the ways to address them is required to support this vulnerable population.

PHYSICAL CHALLENGES

Short- and long-term symptoms experienced by cancer survivors can be debilitating. These include hair loss, pain, swelling of arms and legs (lymphedema), joint pain (arthralgia), insomnia, nausea, vomiting, and loss of smell and appetite. Long-term effects of cancer and cancer treatment include heart damage (cardiotoxicity), lung (pulmonary) damage, loss of bone density (osteoporosis), excess body fat, nerve issues (peripheral neuropathy), cognitive decline, infertility, and sexual dysfunction as well as development of secondary cancers (see sidebar on **Phases of Cancer Survivorship**, p. 103).

One important area of ongoing research is to determine how certain cancer therapies lead to premature aging (396). Research has shown that cancer survivors have an "excess heart age"—a measure of cardiovascular damage and risk for a heart attack—of eight and a half years in men and six and half years in women compared to those individuals who have never

Phases of Cancer Survivorship



Although cancer survivors may face challenges, some groups are at higher risk for severe and long-term and late effects.

This includes those diagnosed during childhood, adolescence, and young adulthood (from ages <1 to 39). Several organizations have established guidelines specifically for AYA patients including National Comprehensive Cancer Network's (NCCN) "Adolescents and Young Adults with Cancer" and The Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers." These guidelines were developed to help standardize and enhance the lifelong follow-up care of individuals who were diagnosed with cancer as children, adolescents, or young adults. For more information, see http://survivorshipguidelines.org/.

This also includes older adults (age 65 and older). The NCCN's "Guidelines for Older Adult Oncology" address specific issues of cancer in older adults, including screening and comprehensive geriatric assessment, treatment risk and benefits, and management of complications from therapies.

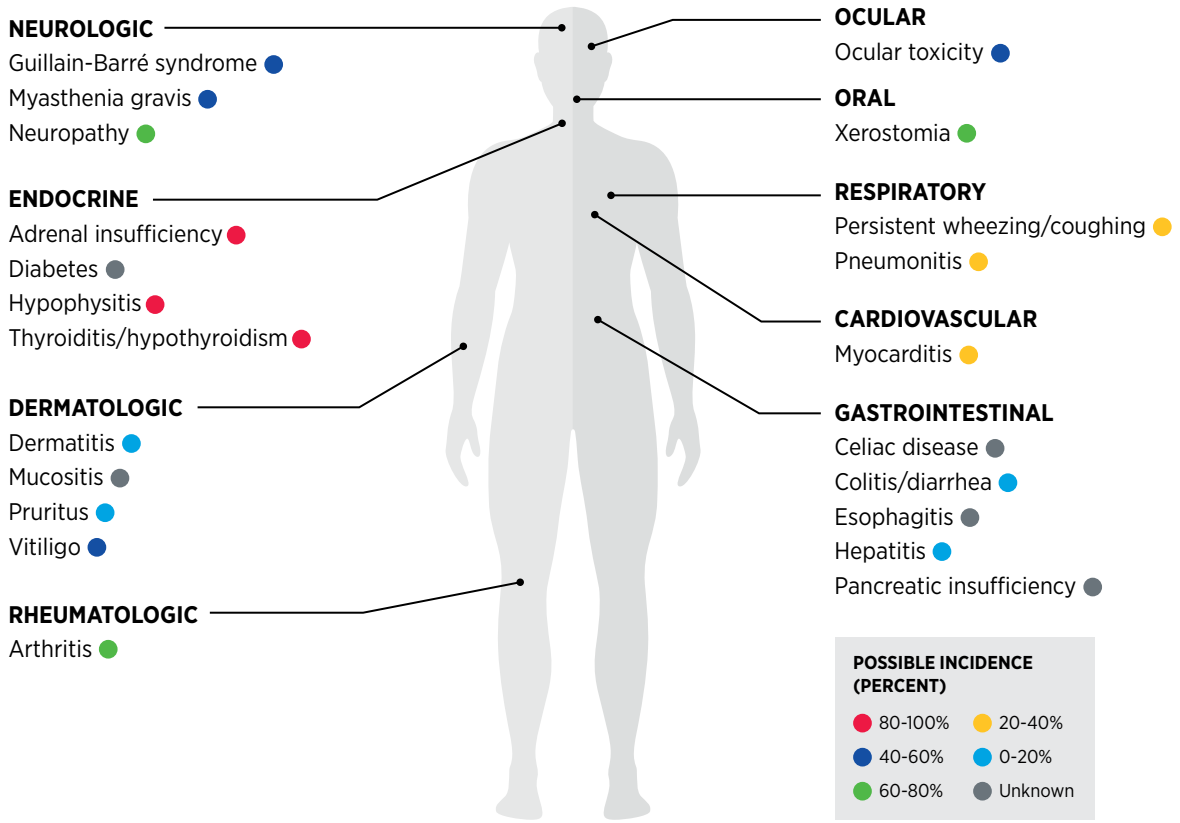
Adapted from (21).

received a cancer diagnosis (397). Notably, average excess heart age was shown to be higher in cancer patients who are NHB, less educated, and have lower income.

The increased use of precision medicine approaches including molecularly targeted therapeutics and immunotherapeutics has led to immense progress in treating cancer. Immune checkpoint

Common Side Effects of Immune Checkpoint Inhibitors

In the past decade, cancer researchers have developed a type of immunotherapy called immune checkpoint inhibitors (ICIs), which are treatments that help the body recognize and attack cancer cells. The success of this treatment has led to many more people living longer, fuller lives. Only now are we seeing the long- and late-term side effects survivors treated with ICIs can develop. Below are some of the more common side effects and the frequency in which they occur.



Adapted from (398).

inhibitors (ICIs) are a type of immunotherapy that is being used increasingly for the treatment of a wide array of cancers. Currently, there are nine ICIs approved by FDA to treat 18 different types of cancer, with some patients achieving highly durable responses. However, their widespread use has also led to concerns about the unique side effects that can result from these treatments. Because these inhibitors attempt to re-establish control of cells of the immune system, frequently observed side effects are autoimmune disorders, such as dermatitis, arthritis, and/or celiac disease (see sidebar on **Common Side Effects of Immune Checkpoint Inhibitors**, p. 104). Furthermore, certain side effects including endocrinopathies (such as hypothyroidism), arthritis, dry mouth, neurotoxicity, and ocular-related effects are more likely to become long-term side effects (398). With the increased use of these drugs resulting in long-term survival, an understanding of their long-term and late effects is necessary.

PSYCHOSOCIAL CHALLENGES

Being faced with a diagnosis of cancer can pose a serious challenge to a person's mental and emotional health. Cancer survivors can experience anxiety (7-21 percent), depression (5-7 percent), and distress (25-41 percent) with higher prevalence among those who are AYA, or belong to racial and ethnic minority and sexual and gender minority populations

The **risk of suicide is twice as high in patients who receive a cancer diagnosis** when compared to the general population. This risk is even greater in those with a diagnosis of cancer with lower 5-year survival rates.

The National Suicide Prevention Lifeline recently established a new three-digit telephone number, 988, to provide free and confidential support for those experiencing thoughts of suicide or distress.

(13,399). It is also concerning that the stress associated with a cancer diagnosis may lead to biological changes that increase cancer progression and recurrence (395,400,401).

Even after successful cancer treatment, anxiety of cancer returning, or the development of new cancers, can lead to distress and/or depression. For instance, in one study that looked at long-term cancer survivors, survivors had higher levels of depression and anxiety after five or more years compared to just after their initial diagnosis (402). Meta-analysis of nurse-led interventions for anxiety management of cancer survivors demonstrate that one-on-one (versus group) approaches over an average of six months for no more than 60 minutes at a time are among the most effective way to help survivors deal with anxiety (403).

A major concern among health care providers is the high risk of suicide in individuals who receive a cancer diagnosis (404). Those who receive a poor cancer prognosis (i.e., low 5-year survival) have the greatest risk of self-harm. The risk of mortality from self-harm was highest within 12 months of diagnosis (405). Proven intervention strategies include the use of psychotherapy (see **Improving Mental Health**, p 111); both nursing and caregiver interventions; and mindful activities including exercise, yoga, and music therapy (406).

Survivors of cancer who are living longer with advanced and metastatic disease are particularly vulnerable to negative psychological challenges. Uncertainty about their prognosis can contribute to apprehension, anxiety, and distress especially during routine follow-up scans; this well-documented phenomenon has led to the term "scanxiety" (407). Currently, there are several NCI-supported studies that are looking at survivorship in individuals living with advanced and metastatic cancers, which will help to identify the best way to support this population (408).

It should be noted that caregivers of cancer survivors often experience burnout due to providing medical and social support for long periods of time. Increasing patient- and caregiver-centric support through psychosocial services, use of accurate prognostic tools, and further research to improve the unique experiences of survivors and their caregivers can help to overcome the challenges faced by these populations.

FINANCIAL CHALLENGES

Financial toxicity refers to the financial hardship associated with cancer treatment and management. Accruing evidence indicates that cancer survivors who experience financial toxicity such as difficulty paying for prescriptions, mental health care, and dental care, and/or who delay medical care due to cost, are also at greater risk of mortality, regardless of insurance status (409).

Financial toxicity is pervasive among patients with cancer. As one example, a recent study that looked at patients with colorectal cancer found that 71 percent experienced a major financial hardship at 12 months after diagnosis (410). Financial toxicity poses challenges not only to the mental and emotional health of those diagnosed with cancer, but also to immediate family members who may depend on the patient for their livelihood.

As of 2019, cancer is the second most expensive chronic health condition in the United States, with patients' out-of-pocket costs and lost work hours totaling $21 billion a year (38). While much of the out-of-pocket costs associated with medical treatment can be covered by health insurance, patients who are enrolled in high-deductible insurance plans face increased expenses compared to those with either traditional plans or with no history of cancer.

One study that compared out-of-pocket costs of individuals on a high-deductible health plan found that those with a history of breast, colorectal, or lung cancer paid an additional $1,683, $1,450, and $467 respectively, compared to those with no history of cancer (411). This is especially concerning because of the estimates that 50 percent of all U.S. adults would have difficulty paying a $400 emergency expense, with 19 percent not being able to pay it at all (412). Patients with other types of cancer are also more likely to miss credit-card payments and to experience other adverse financial events because of missed debt payments (413).

The inability to afford treatments often leads to coping behaviors such as skipping drug doses or not filling prescriptions; increased anxiety, stress, and depression; and forgoing spending on essentials such as food and clothing (414). However, one study looking at lung cancer patients after six months of receiving treatment found that while 28 percent had to make financial sacrifices, only five percent refused medical care based on cost (415). While this number is low, cost of treatment should never be a factor that prevents someone from receiving lifesaving care. Solutions to help those who are unable to afford treatment need to be explored to bring equitable access for all.

Those experiencing financial toxicity are also less likely to enroll in clinical trials, reducing access to potentially lifesaving

treatments (416-418). To reduce the financial impact and help those cancer patients who have low household incomes, direct reimbursement of costs associated with clinical trials was found to significantly improve patient well-being, decrease vulnerability, and help protect right to equal treatment (419).

Recently, time toxicity, which is the amount of time a patient must devote to treatment, has been highlighted as an increasing challenge faced by survivors. This includes things like traveling to and from a treatment center, clinical and physical assessments, tumor assessments, infusions, and patient-reported assessments. In a study of nine clinical trials, researchers found that patients on active treatment spent a median of 16 hours distributed over 4-5 days on trial-related activities every month (420).

UNIQUE CHALLENGES FACED BY VULNERABLE POPULATIONS

Adolescents and Young Adults

Adolescent and young adult (AYA) cancer survivors include those diagnosed between the ages of 15 and 39 and can face unique personal, social, and emotional challenges. Eighty-five and a half percent of AYA survivors are alive at least five years after diagnosis in 2018, compared to only 68 percent of adolescent survivors 40 years ago (421).

AYA populations are more vulnerable to certain side effects including stroke, neurodegenerative disorders, cardiovascular disease, diabetes, and other pulmonary diseases compared to their peers who have not had a cancer diagnosis (422-424). Compared to the general population, AYA cancer survivors are nearly twice as likely to die from a subsequent primary cancer, stressing the importance of increased surveillance in this population (18).

Many treatments for cancer, including surgery, radiotherapy, and cytotoxic chemotherapy, can cause male and female infertility, which is the inability to conceive a child. Loss of fertility is a significant concern among AYA cancer survivors and their caregivers, and can affect their psychological well-being, choice of treatments, and treatment adherence. According to a meta-analysis, between 44 and 86 percent of AYA survivors had moderate concerns about how cancer treatment would affect their fertility, while 28 to 44 percent had severe concerns (425).

The possibility of impaired reproductive abilities may lead some patients to store reproductive material through the process of fertility preservation (see sidebar on **Fertility Preservation After a Diagnosis of Cancer**, p. 106). Rates of fertility preservation vary based on a patient's age, sex, type of cancer, and treating institution. Participation in fertility preservation and what type of preservation should be sought are to be decided by the individual after discussions with the health care providers.

Unfortunately, fertility preservation rates are lower in survivors who are Black, poor, or live in rural areas. Currently, cancer-focused organizations have guidelines that recommend discussions of fertility preservation and sexual health as an essential part of cancer management, especially in AYA patient populations. Furthermore, as of June 2022, 12 states have mandates, and three have active legislation, requiring insurance coverage of fertility preservation for patients facing infertility due to treatments such as anticancer therapies (426).

The Supreme Court's decision on the *Dobbs v. Jackson Women's Health Organization* case in June 2022 has led to serious concerns about how states may regulate embryonic material, which may affect access to fertility preservation services such as sperm and egg banking, banking of embryos, and *in vitro* fertilization by patients with cancer. For patients who may wish to become pregnant, conversations about fertility preservation

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 occur in 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 being treated with radiotherapy

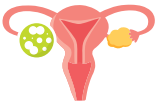
GIRLS AND WOMEN

- Banking of ovarian tissue
- Banking of eggs
- Banking of embryos
- Surgically moving ovaries away from areas of radiotherapy
- Removing cervix but preserving uterus
- Shielding of ovaries from radiation if being treated with radiotherapy

Adapted from (86).

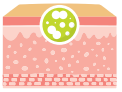
One in 2000 women will experience cancer concurrent with pregnancy (427).

CERVICAL CANCER
One percent of pregnant women (428).



OVARIAN CANCER
Three to six percent of pregnant women (429).

BREAST CANCER
Three percent of pregnant women (430).



MELANOMA
Eight percent of pregnant women (431).

and family planning are an essential early step to treatment and require careful, unrestricted conversations between patient and health care providers.

A recent population-based study of more than 42,000 women ages 16 to 49 indicates that about one in 2,000 pregnancies is complicated by cancer (427). It has been well documented that some cancer treatments, such as chemotherapy, radiation therapy, and targeted therapies have varying risks to both mother and the developing embryo or fetus, with some preclinical and clinical evidence indicating high risk of fetal malformation or spontaneous abortion depending on the stage of pregnancy, type of therapy, and type of cancer (see sidebar **Pregnancy and Cancer**, p. 108).

With the recent Supreme Court decision to overturn *Roe v. Wade*, which ends the constitutional right to an abortion, there is uncertainty surrounding how a particular cancer treatment may lead to the termination of a pregnancy. Such uncertainty may prohibit some physicians from prescribing a drug or performing other health services in a timely manner due to the potential legal consequences for both physician and mother. AACR as well as many other cancer advocacy organizations is extremely concerned about the ramifications of the *Dobbs v. Jackson Women's Health Organization* decision and the effect it could have on access to equitable quality health care. A reluctance or delay in starting treatment could lead to cancer progressing to an advanced stage, thus making the cancer more difficult to treat. Understanding the effects of limited options for health care interventions for pregnant women with cancer needs to be prioritized to provide the best care for this population.

Apart from physical side effects, the disruptive nature of a cancer diagnosis also impacts social development, psychological health, and career development. Together, these result in poorer health-related quality of life (HRQOL) and a greater psychological distress among AYA cancer survivors compared to those who have never received a cancer diagnosis (446,447)

Also contributing to poorer HRQOL is financial toxicity, with AYA cancer survivors at a greater risk of experiencing financial toxicity compared to older survivors (448,449). AYA survivors who live at or below the federal poverty threshold have decreased survival compared to those above (450). AYA survivors who are diagnosed with a psychological disorder are more likely to have increased medical expenses compared to their peers who did not experience a psychological episode (447).

After conclusion of treatment, AYA patients often have trouble with follow-up care, which can impact future screening for recurrent or new cancers and management of side effects. For some, getting transportation to follow-up care can be difficult. Promisingly, new evidence reveals that the implementation of telehealth strategies that were necessitated by the COVID-19 pandemic has helped mitigate transportation challenges and improve follow-up care specifically among AYA cancer survivors (451).

Current guidelines during end-of-life care favor focusing on HRQOL over intense treatment interventions, which can be aggressive, invasive, and expensive. Unfortunately, one study that looked specifically at treatment intensity found that AYA cancer patients received increased frequency of intense interventions, such as the use of mechanical ventilation or admittance to intensive care units (452).

Older Adults

Older adults are defined as those age 65 and over and represent 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 (453).

11.5 percent of AYA cancer survivors reported **psychological distress more than 20 years after** the initial cancer diagnosis (447).

Annual **medical expenses related to psychological distress in AYA cancer survivors** were, on average per person, **$2,600 higher** compared to adults without a history of cancer (447).

Pregnancy and Cancer

EFFECTS OF CANCERS ON PREGNANT WOMEN

- A study that included 1,047 women diagnosed with cancer either during pregnancy or immediately thereafter revealed that there were **differences in outcomes depending on the type of cancer** with which the woman was diagnosed and whether the diagnosis occurred during pregnancy or after birth (427).
- **Hormonal and blood volume changes** that occur during pregnancy **can affect how a drug is metabolized** by the mother and may lead to under- or overdosing (432).

EFFECTS OF CANCER THERAPIES ON PREGNANT WOMEN

Studies have reported that:

Cancer treatments including **chemotherapy, radiation therapy, and surgery led to a 54 percent increase in preterm births**, of which 51.2 percent required admission of the baby to an intensive care unit (433).

- Preterm babies born to mothers who received cancer therapy when pregnant showed **worse cognitive outcomes** compared to babies born at term to mothers who had not received chemotherapy (434).

EFFECTS OF CHEMOTHERAPIES ON PREGNANT WOMEN

Chemotherapies that have been studied in pregnant women include antimetabolites (aminopterin, methotrexate, and cytosine arabinoside) and alkylating agents (chlorambucil, mechlorethamine, and cyclophosphamide) among others.

- **During the first three months of pregnancy**, the **risk of birth defects or miscarriage** from exposure to chemotherapies is high (435).
- The administration of chemotherapy **during the first trimester** led to **increase in malformations in the fetus** (seven to 17 percent increase with a single agent, and a 25 percent increase with chemotherapy combinations) (436).
- Chemotherapy **during the later stages of pregnancy** can lead to low blood count, which may **increase the risk of infection for the mother**, placing the health of both mother and child at risk (432).
- **During the second and third trimesters**, the **placenta can act as a barrier to protect the developing fetus** from some drugs. Current evidence is highly variable regarding the risk of malformations, side effects, and spontaneous abortion, and indicates that the **outcome depends on type of treatment, cancer type, and when treatment started or ended**, underscoring the need for additional studies with a larger patient population (434,436-439).

EFFECT OF OTHER TYPES OF CANCER TREATMENTS ON PREGNANT WOMEN

Surgery

Generally safe for pregnant women. However, some surgeries, such as hysterectomy for cervical cancers, will lead to the termination of pregnancy. Similarly, when anesthesia is required for surgery, it carries the risk of several complications, including an increased risk of miscarriage during the first trimester (440-442).

Radiation therapy

At low doses is considered safe and is not associated with an increase in birth defects as long as precautions are taken to protect the fetus against radiation (443). Higher doses are not recommended.

Immunotherapies and molecularly targeted therapies

Have become a part of routine cancer care only in the past decade, and there are very few preclinical or clinical data on how these treatments alone or in combination may affect pregnancy, the fetus, or fertility:

- There have been just seven reported clinical cases of negative effects as a result of the use of immune checkpoint inhibitors in pregnant women, however, these effects resolved resolve within six months (444).
- Molecularly targeted therapies including trastuzumab, imatinib, ATRA, dasatinib, and nilotinib have been shown to lead to major malformations or spontaneous abortion when administered in the first trimester (445).

70 percent of cancer **survivors over the age of 75** report **at least one comorbidity** (458).

However, studies of this population of cancer survivors are rare (454). More attention and resources are needed to understand the unique challenges faced by older adults.

Cancer and its treatments can lead to side effects that are experienced differently in older adults when compared to those younger than age 65 (455). Evidence shows that 25 percent of older adults with cancer have five or more comorbid conditions (e.g., arthritis, diabetes, or mental health) (456). Older adults may also be prescribed multiple medications to treat other conditions with 22.4 percent of U.S. adults using at least five prescription drugs at a time (457), which leads to safety concerns of adverse drug effects, harmful drug interactions, and drug-disease interactions, in which a medication prescribed to treat one condition worsens another or causes a new one.

Cognitive decline is greater in older adults following treatment, with this group more likely to see declines in executive function and verbal memory. In a recent study, it was found that despite showing high levels of cognitive function at diagnosis, older adults were more likely to experience cognitive decline post-treatment than those younger than age 65 (459).

Older adult survivors also experience poorer HRQOL compared to those under the age of 65 with variations depending on the type of cancer, side effects, frailty, fatigue, and health status. Psychosocial variables such as depression, reduced optimism, chronic stress, and lack of emotional support also influence HRQOL in older adult cancer survivors compared to adult survivors. HRQOL is also worse in groups who are of low socioeconomic status (459).

There is emerging evidence that a comprehensive geriatric assessment of patients at the time of diagnosis can help in planning appropriate interventions by evaluating their functional ability, physical health, cognition and mental health, and socio-environmental circumstances (460). Comprehensive geriatric assessments are not widely utilized because they are often taxing and time-consuming for both patients and providers (458). Therefore, increased support through support staff and a multidisciplinary team are essential for successful implementation of comprehensive geriatric assessments (461).

Racial and Ethnic Minorities and Other Underserved Populations

Individuals from racial and ethnic minority groups and other underserved populations have been found to experience side effects at higher rates than those who are White. The adverse physical effects, coupled with worsened functional, psychological, social, and financial challenges, contribute to poorer HRQOL. As one example, the development of breast cancer-related lymphedema, which occurs after damage to the lymphatic system during surgery, occurs 3.85 times more often in Black women and 1.47 times more often in Hispanic women (462). Lymphedemas are often painful and require the use of special equipment to manage symptoms. These types of challenges lead to lower overall HRQOL in cancer survivors compared to individuals who have never had a cancer diagnosis, especially in medically underserved groups.

Financial toxicity is more prevalent in individuals from disadvantaged groups such as those of low socioeconomic status, further exacerbating their economic hardship. As one example, Black and Hispanic patients with cancer experience adverse financial events twice as often as White patients, leading to increased use of financial coping behaviors, such as skipping medications (463).

Consequences of financial toxicity including food insecurity, which is a lack of access to enough food for an active and healthy life, and unequal access to safe and adequate housing and are prevalent in low-income, racial and ethnic minority, and immigrant survivors of cancer.

Understanding the challenges faced by these groups will help inform cancer care strategies and personalized recommendations to support those who are more vulnerable, and may lead to better HRQOL. The release of the *AACR Cancer Disparities Progress Report 2022* summarizes the inequities in survivorship experiences among these population groups and outlines concrete steps to charting a path forward (13).

Improving Health-related Quality of Life and Outcomes

PROMOTING HEALTHY BEHAVIORS

Certain lifestyle changes can significantly improve both cancer outcomes and HRQOL for cancer survivors. These include eliminating tobacco use, adopting a healthy diet, increasing physical activity, and reducing alcohol consumption.

Cancer survivors who incorporate routine exercise into their life (see sidebar on **Physical Activity Guidelines**, p. 36) can significantly improve survival from several types of cancer including breast, colon, and prostate (464,465), while a sedentary lifestyle is associated with an elevated risk of cancer-related mortality (466). Studies also demonstrate that incorporation of physical activity can reduce cancer recurrence by half compared to those who do not participate in exercise (467,468).

Physical activity may also alleviate certain adverse side effects experienced by cancer survivors. For instance, one study from the United Kingdom found that breast cancer survivors who participated in regimented physiotherapy over three months had reduced upper limb disability after one year compared to

One study of 1,500 cancer survivors conducted over a nine-year period found that **survivors who were active had 66 percent lower rates of all-cause mortality** compared to those who led a sedentary lifestyle (466).

Smoking cessation after a cancer diagnosis can **increase five-year survival** by 12 percent and **reduce progression of cancer** by 10.6 percent (485).

those who did not receive structured exercise therapy (469). Studies also demonstrate that exercise can improve bone and spine health in patients with cancer (470,471). Furthermore, moderate exercise can reduce cardiovascular risk factors by up to 33 percent, as reported in a study of long-term breast cancer survivors (472). This is especially relevant because cardiovascular disease is the primary cause of non-cancer-related deaths in breast cancer survivors, accounting for mortality in 35 percent of breast cancer survivors age 50 or older (473).

Initiatives such as the Get Up, Get Moving program from the Oncology Nursing Society, which provided at-home, personalized physical activity coaching and electronic activity trackers to cancer patients, can promote increases in physical activity and help reduce common side effects such as nausea from cancer treatments (474).

Preliminary studies in animal models show that exercise during active treatment with cancer immunotherapy can reduce disease progression and mortality (475). In the Preoperative Rehabilitation During Neoadjuvant Therapy for Pancreatic Cancer clinical trial, pancreatic cancer patients who exercised prior to surgery had more immune cells which were associated with tumor elimination. The trial, which began in 2017, has also shown that there is a 50 percent higher five-year survival rate for those who exercise compared to those who do not (476,477).

Sustaining a healthy diet that consists of whole grains, fruits, and vegetables can increase survival from cancer and reduce the risk of cancer recurrence (478). Multiple population-based studies with evidence collected over the past 20 years from survivors of prostate cancer show that in addition to smoking and diets with high saturated fats, consumption of greater than four servings per week of whole milk and/or high-fat dairy products following a diagnosis of prostate cancer was associated with higher risk of prostate cancer recurrence and mortality (465).

Poor diet, which can contribute to other chronic health conditions such as diabetes, can negatively impact survival from cancer. In one study of long-term survivors of metastatic breast cancer, 10 years after diagnosis, those who had diabetes had 20 percent lower rate of survival compared to those who did not have diabetes. Furthermore, of those with diabetes, those with better management of blood sugar levels had 20 percent higher rates of survival compared to those who did not manage their blood sugar levels (479).

As discussed in earlier sections, maintaining a healthy diet can often be a challenge for cancer survivors, particularly those from low-income, immigrant, and other vulnerable populations, because of food insecurity. One clinical trial that provided food voucher programs in combination with access to a food pantry improved outcomes for food-insecure cancer patients with 95 percent completing their prescribed cancer treatment. This outcome was compared to those who only had access to a food delivery service and food pantry or to just the pantry alone, with an 83 percent or 78 percent treatment completion rate, respectively (480). It is imperative that survivorship interventions screen for food insecurity and provide cancer patients and survivors with necessary services which increase treatment completion and improve HRQOL.

Decades of evidence indicate that smoking cessation after a cancer diagnosis can improve clinical outcomes by increasing survival, reducing drug interactions, and improving quality of life after treatment. All major cancer-focused professional organizations recommend smoking cessation after a cancer diagnosis (481-484).

Although smoking cessation can be difficult for some patients, intensive programs that provide counseling and FDA-approved medication are both cost effective and highly effective in smoking cessation (486).

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, psychological, financial, social, and spiritual needs that arise from the disease and the treatments (see sidebar on **What Is Palliative Care?**, p. 111). Palliative care is facilitated by a multidisciplinary team 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 (487).

Integration of palliative care during the early stage of a person's cancer experience can significantly improve HRQOL. Multiple studies have reported that palliative care leads to improved management of symptoms resulting from cancer and/or its treatment, decreases depression and anxiety, reduces financial toxicity, improves HRQOL for both cancer survivors and their caregivers, and results in longer survival (488-491).

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 not the same as hospice care, because it 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 can be given in addition to cancer treatment or to those with no curative treatment options; palliative care given near the end of life when curative treatment has stopped is usually referred to as hospice care.

Palliative care addresses many of the challenges that can affect quality of life after a cancer diagnosis, including:

- Emotional challenges, such as anxiety and depression.
- Physical symptoms and adverse effects of the disease and its treatment, such as pain, nausea, vomiting, fatigue, difficulty sleeping, and loss of appetite.
- Practical challenges, such as navigating the health care system.
- Spiritual challenges.

Adapted from (86)

In one clinical trial of patients with acute myeloid leukemia it was found that the use of a palliative care team early on in treatment with intensive chemotherapy led to increased practice of coping strategies among patients. These coping strategies led to a reduction in depression and anxiety symptoms and better HRQOL in this group compared to those who did not receive palliative care (491).

Due to the increased risk of financial toxicity among cancer patients and survivors, interventions to alleviate this risk must be explored. Despite the prevalence of financial toxicity, oncologists are often not prepared to engage in these conversations necessitating increased training or alternative strategies (492,493). For instance, one study found that palliative care teams could help screen for financial hardship early on in care (494). Interviews with patients have revealed that these discussions, held with trusted individuals who provide emotional support and understanding, can help alleviate anxiety about the financial challenges of cancer treatment and survivorship (495).

IMPROVING MENTAL HEALTH

The psychological challenges faced by survivors of cancer necessitate approaches that improve the mental well-being of this population (see **Challenges Faced by Cancer Survivors**, p. 102). One promising area is psycho-oncology, an interdisciplinary subspeciality within the cancer care continuum that aims to address the physical, behavioral, emotional, and psychosocial distress that arises for cancer survivors and their caregivers (496). Experts who are trained in psycho-oncology apply a holistic approach to destigmatize and address behavioral and psychosocial distress that is often caused by cancer diagnosis and treatment (see sidebar on **Helping Patients with Cancer Through Psycho-oncology Research**, p. 112).

Participating in face-to-face or online group positive psychotherapy, an approach that focuses on increasing resilience and a sense of well-being for cancer survivors, significantly reduced symptoms of emotional distress and improved mental well-being among cancer patients (499).

Researchers are also trying to understand how survivors of cancer experience post traumatic growth, which describes the positive life changes that can develop out of traumatic, stressful events such as a diagnosis of cancer. This type of growth includes perceptions of new possibilities, closer relationships with family and friends, development of personal strength, spiritual development, and a greater appreciation for life (500). Although the concept of post-traumatic growth is not new, it is just beginning to be appreciated within the cancer community to understand how to foster these positive outlooks in survivors and improve mental health. The most influential factors that affect post-traumatic growth include the level of social support and the use of various coping strategies among survivors of cancer (see sidebar on **Coping With Post-Traumatic Stress After a Cancer Diagnosis**, p 113).

Delivering Care to Cancer Survivors

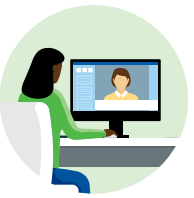
COORDINATING CARE

The multifaceted approach to treating cancer means providing survivors with care to address their many needs including transition from active treatment; coordinating follow-up appointments; addressing financial needs; and access to other survivorship resources. While these resources are often available, understanding how or where to gain access to them can be

Helping Patients with Cancer Through Psycho-oncology Research

The field of psycho-oncology comprises psychiatrists, psychologists, nurses, and social workers who are dedicated to addressing the behavioral, emotional, psychological, and social challenges faced by cancer survivors and their caregivers. Approaches to helping these individuals tested in recent clinical trials include:

Physical exercise (aerobic, resistance training, running, and free weights), **psychological interventions** (cognitive-behavioral therapy, psychoeducational interventions), **and mind-body interventions** (yoga, mindfulness, hypnosis) have been shown to be effective at mitigating or reducing cancer-related fatigue and sleep disturbances among patients with cancer (497).



Participating in a computer-based, 12-week-long cognitive rehabilitation program during and after chemotherapy significantly improved cognitive abilities and working memory, and reduced symptoms of depression and anxiety among cancer patients (498).

challenging (505); this necessitates the coordination of care for patients to help them identify and gain access to such resources.

Coordinated cancer care is most effective when a designated care coordinator, an individual or a team of people such as patient navigators, helps a patient with cancer or a survivor of cancer in getting access to the resources they need. A meta-analysis looking at 30 years of empirical evidence of coordinated cancer care, often through patient navigation, showed there was an 81 percent improvement in outcomes for patients and reduced costs associated with care (506).

Clinical follow-up programs are an important first step to help coordinate care for survivors of cancer. These include active surveillance programs, standardization of protocols among stakeholders, and follow-up through telehealth methods. In an analysis of colorectal cancer patients, implementation of the previously mentioned strategies reduced readmissions at 30 days by 32 percent and significantly reduced the time spent in the hospital by one and a half days (507).

Cancer survivors with **low health literacy** were **five times more likely to have improved physical quality of life** when they were **assigned a cancer care coordinator** (508).

SUPPORTING CAREGIVERS

Caregivers comprise family members or friends who help patients with long-term, chronic illness manage all aspects of their care. One in five U.S. adults (ages 18 to 64), which is over 43 million people, provided care for another person in 2020 (509). It is estimated that four million of these caregivers are caring for an adult cancer patient. More evidence surrounding the challenges faced by this population is becoming clear and there are many opportunities to assist this vulnerable group.

Of the 43.5 million caregivers, only 60 percent had been employed in the previous 12 months (509). Nearly half of employed caregivers reported challenges with maintaining normal job hours, with 24 percent reporting reduced work hours and 11 percent retiring early (510).

Paid leave can allow caregivers to help family with long-term illnesses such as cancer. Unfortunately, 77 percent of U.S. workers do not have access to paid leave, forcing workers to take unpaid leave, which results in lost income that can be detrimental to a family's financial health, potentially leading to financial toxicity (511). Financial toxicity among caregivers leads to higher rates of nonadherence to cancer care, increased lifestyle-altering behaviors, and worse quality of life in both patients and caregivers (507).

Paid leave could keep more than 6 million caregivers in the U.S. workforce by 2030 who otherwise would not have returned to work after providing care for their loved one (509).

Coping With Post-Traumatic Stress After a Cancer Diagnosis

Both quantitative and qualitative data demonstrate that most cancer survivors experience post-traumatic growth, which is described as the personal growth that comes from experiencing a stressful, traumatic event (496-498). Post-traumatic growth is not necessarily a consequence of a traumatic event and to experience post-traumatic growth, survivors need to cultivate these feelings through personal development (499). Post-traumatic growth is being more appreciated as an approach to improve a survivor's mental well-being and recovery. Components of post-traumatic growth include:

RELATING TO OTHERS

Survivors find that their cancer diagnosis helped them prioritize and improve relationships and build stronger connections with those who are important to them. These experiences are attributed to increased willingness to express feelings, understand complex emotions, and better empathize with those struggling with similar challenges.

NEW POSSIBILITIES

Often described as a completely new lifestyle after cancer diagnosis, survivors may re-evaluate 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

Living with and beyond a cancer diagnosis presents survivors with an immense challenge. While enduring such a difficult time, survivors may experience a belief that if they are able to defeat cancer, they can possibly manage any future challenge. This can prompt positive attitudes during times of stress or anxiety.

NEW APPRECIATION OF LIFE

Reevaluation of what it means to be in good health leads many survivors to describe feelings of appreciation of good health, a second chance at life, appreciation of the beauty in the world, and gratefulness for the small victories in life. Others report having the perspective of living in the moment.

SPIRITUAL CHANGES

Receiving a cancer diagnosis can lead to finding or strengthening of spiritual beliefs and a deepening of faith. Spiritual growth has also been shown to help survivors with their recovery and the ability to manage day-to-day challenges.

Adapted from (501).

Evidence indicates that implementation of paid leave reduces household income volatility, facilitates reemployment, and leads to more workers reentering the labor force (513). Currently, there is no federal paid leave plan and only 12 U.S. states have or will implement programs by 2026 (514). By 2030, the number of caregivers is expected to increase by 9.3 million. To preserve the U.S. labor force and ensure optimal health for cancer patients and their caregivers, it is vital that better paid leave policies are implemented.

IMPLEMENTING TELEHEALTH

The COVID-19 pandemic led to a meteoric rise in the use of telehealth for all aspects of patient care (see sidebar on **What Is Telemedicine?**, p. 114). The use of telemedicine by older adults and patients with cancer has already had a widespread positive effect on the delivery of oncology services during the pandemic and has allowed patients to continue receiving cancer care, even when they are unable to visit a health care

What Is Telemedicine?

According to NCI, telemedicine, also called telehealth, is the delivery of health care from a distance using electronic information and technology, such as computers, cameras, videoconferencing, satellites, wireless communications, and the Internet.

TYPES OF TELEMEDICINE

Teleconsultation Presentation of a patient's health report by the primary health care provider(s) to an expert in another institution.

Telediagnosis Remote or concurrent transmission of results from physical exams, scans and/or lab tests to a specialist, such as a pathologist, for diagnostic purposes.

Teleinterpretation Interpretation of a patient's test results, such as images obtained from a full-body scan, remotely.

Telemonitoring Signs or symptoms, as well as health records, of a patient communicated to a health care team by an electronic communication platform that is compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Telesupervision Presentation of a patient's information via shared screen electronically—either recorded or with the patient present in person—to a senior clinician by a medical trainee (e.g., medical student) or other health care worker (e.g., nurse) using electronic means, such as PowerPoint slides.

Televisit Usual visit of a patient with his or her health care provider but using videoconferencing software.

POTENTIAL BENEFITS OF USING TELEMEDICINE

- **Increased access to health care** Allows access to health services that may not be available to patients locally.
- **Improved health care outcomes** Promotes continuity of care regardless of the location of the patient and the provider, thus improving overall health outcomes.
- **Decreased infectious exposure** Helps avoid exposure to infectious viruses, bacteria, and other pathogens.
- **Reduced costs and/or work-related adjustments** Saves time and money by eliminating the need to travel to the health care facility or to take too much time off work or to arrange for elder and/or childcare.
- **Facilitated caregiver and family engagement** Allows caregivers and other family members to join, which can facilitate patient care.

POTENTIAL DRAWBACKS OF USING TELEMEDICINE

- **Widened health care disparities** Infrastructure that enables electronic communications, such as broadband Internet, computers, or smart phones, as well as digital literacy, are two key requirements for implementing telemedicine effectively. However, lack of access to both is disproportionately experienced by patients from medically underserved populations and may widen already existing disparities.
- **Rapidly changing policies and reimbursement rules** The fast-paced nature of telemedicine may make it harder for health care providers to keep up with health care laws, reimbursement policies, and privacy protections.
- **Costly initial implementation** Implementing telemedicine at a health care facility, including restructuring information technology staff, purchasing necessary equipment, and training clinicians and support staff, takes time and costs money.
- **Security of personal health data** The security of personal health data transmitted electronically is also a concern, which can be mitigated by employing a HIPAA-compliant telemedicine platform.

Adapted from (8).

facility in person (8). Current data indicate that there is overwhelming support by both cancer survivors and providers for the delivery of various types of survivorship care services with telehealth. These services include laboratory results or imaging, management and treatment of cancer symptoms, nutrition counseling, and patient navigation support (516). Use of telehealth also led to increases in quality of life compared to usual care methods (517).

94 percent of patients said their **issues and questions were addressed well through a telehealth visit**, while two thirds said their issues were very well addressed (515).

Looking to the Future of Cancer Science and Medicine

IN THIS SECTION YOU WILL LEARN:

- Better technologies and lower costs have led to the ability of sequencing individual cancer cells allowing researchers to unravel the complexities of cancer.
- Researchers are developing tools to detect pre-cancers and intercept cancers before they develop.
- Use of the immune system to fight cancer has become one of the most promising areas of cancer research. Current efforts are focused on developing immunotherapies that work in various ways for more types of cancers and increasing the robustness of these therapies.
- Artificial intelligence (AI) is utilizing the power of computation to help clinicians and pathologists better diagnose and treat cancer. AI is also assisting researchers in decoding cancer's complexities and answering some of the most elusive problems such as tumor heterogeneity.

Advances in cancer science and medicine over the past decade have contributed to more people living through and beyond their cancer, which brings much excitement and anticipation for what will come in the next decade. **AACR President, 2022-2023, Lisa M Coussens, PhD, FAACR**, is thrilled about what the future holds and is confident that the steady progress toward reducing the burden from all cancers will continue for years to come (see p. 118). Scientific progress against cancer involves efforts from multiple scientific disciplines through national and international collaborations. The new wave of scientific and technological innovations (see sidebar on **Technologies Driving Progress Against Cancer**, p. 117) driven by cross-disciplinary team science will have a transformative impact on patient care. The following sections highlight what the future of cancer care may look like based on the new technologies that are being developed right now.

Looking at Individual Cells

By some estimates, a tumor the size of a pea contains about one billion cells which include cancer cells with a range of genetic and epigenetic alterations as well as other cell types such as immune cells and cells that make up blood vessels called endothelial cells (518). This cellular diversity, also called heterogeneity (see **Tumor Heterogeneity**, p. 24), leads to genetic diversity within tumors and can contribute to treatment resistance and disease recurrence. Currently, standard practice for genetically profiling a patient's tumor is to take a biopsy of tissue and sequence the DNA of all the cells together. We now know that this broad stroke approach overlooks the complex changes that happen within the individual cells of the tumor, each with unique DNA mutations.

Overcoming this heterogeneity presents an immense challenge (see **Tumor Heterogeneity**, p. 24). Promisingly, scientific research has led to extraordinary progress in the development of less expensive, faster, and higher quality technologies that researchers can use to isolate and profile individual cells from a tumor. These technologies have opened new frontiers for decoding cancer's complexities, e.g., understanding how individual cells or small subgroups of cells contribute to cancer initiation, progression, and metastasis.

SINGLE CELL PROFILING

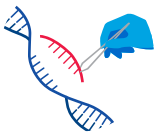
Single cell sequencing is a powerful technology that uses a machine to separate thousands to millions of cells and sequence the genetic material of each cell independently; this increases the resolution of the cellular differences within a diverse population of cells, such as in a tumor. As one example, in a recent study using single cell sequencing of 300,000 lung cancer cells, researchers evaluated the functional impact of a range of alterations in common cancer-causing genes such as *TP53* and *KRAS*. By analyzing the resulting changes in the RNA levels, the researchers aim to better understand how different mutations in the two genes contribute to cancer development (527). Other groups have sequenced RNA instead of DNA, which gives an accurate perspective on what a cell is doing functionally. These data can compare how RNA molecules are expressed in a tumor differently when compared to a healthy cell and this knowledge can help clinicians make decisions on treatment strategies (528,529). In one study of HBV-associated hepatocellular carcinoma, researchers sequenced the RNA of both the tumor cells and the immune cells to understand how spatial interactions between these cell

Continued on page 120

Technologies Driving Progress Against Cancer

Technology drives advances in cancer research and patient care. The following represent emerging state-of-the-art technologies that are poised to transform our basic understanding of cancer development and transform patient care in the near future:

CLUSTERED REGULARLY INTERSPERSED SHORT PALINDROMIC REPEATS (CRISPR)-CAS9 SYSTEM



Revolutionary gene editing approach to help researchers modify the genome precisely and study the impact of the modification on cellular function.

Example of use in cancer:

'Designer' CAR T cells, tailored for a patient's specific cancer, are being developed using CRISPR-Cas9 system (519).

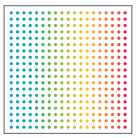
PROTEOLYSIS TARGETING CHIMERAS (PROTACS)

A class of therapeutics to help researchers precisely degrade disease-causing proteins.

Example of use in cancer:

PROTACs to degrade otherwise difficult to target cancer-causing proteins, such as p53, STAT3, RAS, MYC, are currently in different phases of preclinical and clinical development (520,521).

SPATIAL TRANSCRIPTOMICS



A technique to help researchers characterize and map gene activity at a single cell level in a sample of tissue, thus delineating the heterogeneity of tumors.

Example of use in cancer:

This technology is being used for the characterization of tumor heterogeneity (522); prediction of tumor progression (523); and identification of complex interactions between tumor and other cell types (524).

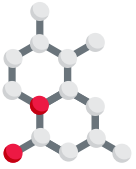
DECONVOLUTING PHENOTYPIC SCREEN HITS

A holistic method to help researchers identify and develop new cancer therapies by investigating alterations in entire biological pathway(s) instead of an individual target, such as a protein.

Example of use in cancer:

Three-dimensional 'organoids' are being grown in laboratories from stem cells or from tumors derived from patients to capture the complexity of an organ or a tumor (525).

SINGLE MOLECULE IMAGING



A method to help researchers diagnose diseases, such as cancer, at an early stage by detecting individual biomarker proteins in patient's bodily fluids.

Example of use in cancer:

The highly sensitive single-molecule augmented capture (SMAC) method can identify miniscule quantities of prostate-specific antigen (PSA) in samples from blood or a solution containing a single prostate cancer cell (526).

Mapping the Future of Progress in Cancer Science and Medicine

LISA M. COUSSENS, MD (hc), PhD, FAACR

AACR President 2022-2023

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There has been tremendous progress in our fundamental understanding of cancer biology during my decades-long career as a scientist. Remarkable discoveries in basic research have led to the development of lifesaving treatments for patients with cancer, resulting in a steady reduction in the overall U.S. cancer mortality rate year after year. I am also very optimistic about the future of cancer science and medicine, because of the new wave of innovations that are just over the horizon and are set to fundamentally improve cancer detection and treatment.

One of the most important lessons learned over the past two decades is that cancer is not a single disease, but a collection of over 200 different types of diseases. We have also learned that, even within a single tumor, a multitude of cell types with different mutations exists. This complexity is one of the reasons that cancers are so difficult to treat. The contributions of the tumor microenvironment, which includes the immune system as well as other cells, further increase the complexity of cancers. With the tremendous boom in sequencing technology over the past two decades, we can further understand these complexities using cutting-edge tools, such as tumor microdissection, single cell sequencing, and proteomics. These technologies have led to an explosion of data, necessitating cross-disciplinary approaches that require cancer biologists, bioinformaticians, computational biologists, and chemists working together to identify the cellular and molecular pathways important for cancer pathogenesis. This type of research is essential for investigators to create drugs to target those vulnerabilities and stop cancer in its tracks. I anticipate that the costs of these sequencing technologies will become even more affordable to the point where personalized medicine approaches are applied to every future patient, dramatically improving their treatment options and transforming patient outcomes.

One area of cancer medicine where we have evidenced unprecedented progress is immune oncology, which leverages the power of immune cells to thwart cancer progression and tumor growth. In particular, the area of adoptive cell therapies, such as CAR T-cell therapies, has changed the treatment landscape for patients with certain hematologic malignancies. We are now beginning to appreciate the potential of other immune cells beyond T cells that can be leveraged to fight tumors, such as natural killer cells and macrophages. Many of these therapies are currently being tested in clinical trials and are set to vastly increase the diversity of immunotherapy options for patients within the next decade. Other immune-based therapies, such as immune checkpoint inhibitors, unleash the power of the immune system to fight cancer, and have improved patient outcomes across many types of cancer. It is important to note that every single advance in developing new and effective treatments for cancer has its roots in a basic research discovery. For instance, the development of checkpoint inhibitors is rooted in the study of basic T-cell biology, which led to the knowledge of the molecular pathways important for their cancer-fighting capabilities, paving the way for this class of immunotherapies.

One of the biggest challenges in cancer research and patient care continues to be the lack of diversity in oncology clinical trials and in genetic databases, such as The Cancer Genome Atlas, which predominantly contains samples from patients of European ancestry. It has been only within the last 25 years that we have begun to appreciate how genetic variants found in populations of shared ancestry contribute to cancer incidence and mortality. Biologists, population scientists, and epidemiologists are working together to decode genetic data and address social determinants of health for better understanding and treatment of cancers in diverse groups of people. In addition to racial and ethnic minorities, increasing our knowledge of the challenges faced by other medically underserved populations, such as sexual and gender minorities and those who are socioeconomically deprived, is required for equitable and culturally appropriate cancer care. Increased funding from our government is necessary to better understand these populations and their unique risk factors so that appropriate intervention strategies can be implemented.

Increasing the participation of medically underserved populations in scientific studies and clinical trials demands a more diverse cancer workforce. While we have made some gains in closing the gender gap in medical science, we still lack racial, ethnic, socioeconomic, and geopolitical diversity. Increasing diversity among researchers and clinicians is crucial for expanding the conversation across the cancer continuum, affording unique perspectives to tackle new questions. I am extremely proud that AACR is playing a leading role in crafting solutions to help increase diversity in cancer research and science by improving the gender balance, as well as by identifying the problems surrounding the lack of diversity.

Basic research is integral to understanding why normal cells become cancerous and it requires continued support both from governmental bodies, such as NIH and NCI, and nonprofit and philanthropic organizations, such as AACR. I often tell my students that you cannot understand how to fix something unless you know why it is broken. Such questions are only addressed through basic research, making it vital that we continually increase our investments in this area. It is these investments that have led to remarkable gains in reducing cancer incidence by implementing effective prevention strategies; in lowering the chances of late-stage disease by detecting cancers earlier; and in reducing cancer mortality by improving treatment options.

"Every single advance in developing new and effective treatments for cancer has its roots in a basic research discovery."

populations changed, which can lead to evasion of cancer cells from the immune system (530).

SUBCELLULAR PROFILING

Some of the most cutting-edge technologies go beyond looking at individual cells and instead examine individual parts of a single cell. One such technology uses an automated laser technique to precisely remove the nucleus of a cell and measure different levels of proteins present (531). This type of research allows scientists to understand not only how each cell of a tumor influences cancer, but also how different compartments within an individual cell can influence a cell's function.

DETECTING THE EARLIEST CHANGES DURING CANCER DEVELOPMENT

Catching cancer early is the best way to prevent it from developing into a more aggressive, harder to treat disease. This often happens during routine screenings, where a precancer, which can be a cell or cluster of cells that could develop into cancer but has not yet, is found and tested. Several research groups are sequencing the genomes of precancerous lesions to identify what mutations are present and if these mutations lead to cancer. For instance, Barrett's esophagus is a disorder characterized by inflammation of the esophagus caused by acid reflux and can often lead to esophageal adenocarcinoma. Researchers identified 80 patients with Barrett's esophagus and sequenced areas of precancer. Of the 80 patients originally identified, 40 developed esophageal adenocarcinoma. When researchers sequenced all 80 patients again, they found that those that developed esophageal adenocarcinoma had changes in the gene *TP53*. Interestingly, the type of mutation found in this gene could be detected up to six years prior to cancer diagnosis (532).

Based on tests like these, recommendations can be made to start or abstain from treatment and opt for surveillance instead. The road from a precancer to cancer is not very well understood, so understanding the path a precancerous cell takes to becoming a cancerous cell, such as looking at *TP53* in Barrett's esophagus, would help inform clinicians about whether to move forward with treatment or not.

Larger research efforts, such as with the Precancer Atlas, are compiling the genetic profiles of precancers into large databases. By studying the different types of mutations that occur in precancerous cells and how those lead to the development of cancer, researchers are understanding more about why this transition occurs and the contribution of both the cancer cell and its surrounding environment.

Artificial Intelligence

Artificial intelligence (AI) is the ability of a machine, often a computer, to do tasks that are normally done by a human and is being used increasingly in cancer science and medicine (see sidebar on **Artificial Intelligence in Early Detection**, p. 53). Previous chapters have highlighted the utilization of AI in cancer screening and diagnosis as well as in increasing the precision of radiation therapy. That is because using AI in the fight against cancer comes from its ability to analyze vast amounts of data that continue to accumulate from around the world, with cancer researchers and clinicians adding new data. Therefore, the future of cancer research, screening, diagnosis, and treatment will benefit greatly from the application of AI.

PERSONALIZING CANCER CARE

The advent of efficient genomic sequencing has led to a revolution in cancer care as we try to understand and personalize treatment specific to patient's characteristics. Listed below are some possibilities:

- Tumor genomics (e.g., **DNA, RNA, and epigenetics**) can be utilized to inform decision-making for the treatment of prostate cancer (533).
- **Tumor genomics** can also assist in grouping of patients for clinical trials and may inform clinical outcomes that are unique to each individual (533-535).
- With the advent of **artificial intelligence software programs** using clinical data and digital imaging from prostate biopsies, prostate cancer therapy can be personalized by predicting long-term, clinically relevant outcomes (536).
- Other emerging technologies include **systems biology-based proteomics** approaches, and **advances in liquid biopsy** approaches that allow detection of multiple cancers from noninvasive tests of bodily fluids, such as blood and urine (537, 538).

AI IN BASIC RESEARCH

To understand how a healthy cell becomes a cancer cell and eventually a tumor, researchers are using AI to look at each individual cell of the tumor to identify the genes that are turned on or off. In a recent study, scientists designed a type of AI program that looked at 9,800 patients with 33 different types of cancer to identify the most common ways the genome becomes

mutated. The algorithm analyzed the "preference" a particular cancer had for a certain type of mutation and used this information to develop a favorites list of common mutations within that type of cancer. This type of algorithm could be applied to new cases of cancer to understand the likelihood that a particular mutation could develop during the cancer's evolution (539).

The vast amount of information gathered from an experiment, thanks to rapid advances in single cell technologies, can make analysis by a person extremely time-consuming and difficult. One study utilized AI to analyze data generated from single cell sequencing to help differentiate breast cancer cells from healthy cells. It went on to group cancer cells based on common characteristics. After AI learned how to do this, researchers were able to apply this more broadly to other cancers, which could aid other researchers in answering questions about cancer evolution (540). With increased use of single cell sequencing technology outlined above, AI approaches will be indispensable to analyze and integrate the vast amounts of data generated.

AI IN DIAGNOSING CANCERS

Diagnosing a cancer typically involves taking a biopsy of tissue and then examining it under a microscope by a pathologist who is trained to find signs of cancer using specialized training and judgment. As this method of diagnosis can be laborious and time-consuming, and can sometimes miss signs of cancer, using AI-based approaches offers a promising way to diagnose cancer.

Currently, studies are exploring the ability of AI to diagnose cancer by comparing results from AI to manual detection done by a pathologist. So far, AI appears to have a high degree of accuracy, even outperforming human pathologists in diagnosing certain types of cancer (541-543). For example, AI was used to detect precancerous colonic polyps, which can develop into colorectal cancer. The researchers found that when AI was used in conjunction with a traditional colonoscopy, this led to a two-fold reduction in missed identification of precancerous lesions compared to diagnoses by a pathologist alone (544). Recently, FDA has approved AI for cancer early detection and diagnosis, demonstrating the effectiveness of this approach (see **Recent Advances in Cancer Screening and Early Detection**, p. 51).

Other approaches that use AI focus on being able to predict the likelihood of developing metastasis. In one study that looked at bone metastasis in patients with breast cancer, an AI algorithm was able to correctly predict the likelihood of bone metastasis 88 percent of the time based on 311,408 different cases (545).

To have the most accurate and equitable AI-based screening approaches, these technologies must be applied to a broad range of groups, including racial and ethnic minorities, especially because there has been a demonstrated bias in the use of AI-based screening approaches in the past. (546-549). For instance, in a meta-analysis of AI programs that were developed to detect melanoma from images of skin lesions, only six out of 136 studies disclosed skin type and only 12 disclosed race and ethnicity. Without inclusion of data on darker skin colors (which are often underrepresented) and reporting of race and ethnicity, AI cannot develop inclusive algorithms, which leads to biased technologies that can have a diagnosis that is inconclusive or false.

The bias often stems from a lack of representation of samples from these groups in the datasets from which the program learns. For instance, The Cancer Genome Atlas is made up of samples predominantly from majority European ancestry, which leads to underrepresentation of prognostic, diagnostic, and therapeutic genetic signatures across races. In contrast, AI algorithms that use data collected from global populations can be applied to broad populations with a high degree of accuracy. For instance, one algorithm called Mirai, was used to predict the development of breast cancer at five years from 128,793 mammograms from 62,185 patients across five countries including the United States, Israel, Sweden, Taiwan, and Brazil. The researchers found that their AI had a high degree of accuracy in predicting breast cancer development, regardless of the country being studied, because of the inclusiveness of the algorithm (549).

Every effort must be made to reduce biases in technologies, which can be done by incorporating a health equity lens early on in development (i.e., incorporating health equity into the AI program); increasing recruitment and representation of a diverse population in AI clinical trials; and implementing reporting standards and auditing (548).

USING AI TO PREDICT TREATMENT SUCCESS

In an age of precision medicine, there are multiple factors including tumor-associated and inherited genetic alterations, lifestyle, environmental exposures, general health, and medical history, many of which evolve over time, that health care providers must consider before selecting the most appropriate therapy (550).

This approach helps to tailor treatment plans to individual patients. In one study that used AI to generate a radiotherapy regimen for prostate cancer, among the 100 patients studied, 89 percent of the radiotherapy treatment plans generated were deemed clinically acceptable, with 72 percent deemed superior to those devised by human experts (551). Another study, which used AI to identify patients with head and neck cancers who would benefit from a reduction in the intensity of their radiotherapy or chemotherapy, showed that AI correctly predicted which patients would benefit from treatment de-escalation (552).

Using the Immune System to Fight Cancer

The immune system can identify and eliminate cancer cells the way it does disease-causing pathogens such as bacteria, viruses, and toxins. The immune system, which is made up of many different types of cells (see sidebar on **Key Cells in**

the Immune System, p. 26), detects foreign objects by using protein sensors on the cell surface. While the immune system is extremely effective in eliminating threats, cancer cells often develop mechanisms to hide from immune cells, escape death, and grow into a tumor. A new class of cancer treatments called immunotherapies utilizes what we know about the immune system to fight cancer. While there has been tremendous progress in this area, immunotherapies do not work for all patients nor are all cancers approved for treatment with specific immunotherapies. In addition, cell-based immunotherapy production is not robust, with long waiting lists for treatment access. This necessitates the discovery of new targets and improved manufacturing technologies. This section details selected examples of what is to come in the research area of immunotherapies and the technologies being developed to expand this type of lifesaving therapy.

THE FUTURE OF IMMUNE CHECKPOINT INHIBITORS

Cancer cells can have proteins on their surface that can turn off certain immune cells when there is contact, thus evading elimination. In the past decade, cancer researchers have developed therapies called immune checkpoint inhibitors that inactivate these proteins and allow the immune system to recognize and eliminate the cancer cell. Unfortunately, only a fraction of patients responds to immune checkpoint inhibitors (ICIs), and many who do respond initially develop resistance over time.

Continued efforts in this area focus on identifying new proteins specific to different cancers and designing drugs to target them, such as the recent FDA approval of nivolumab and relatimab-rmbw (Opdualag), which targets the protein LAG-3 on the surface of T cells, to treat melanoma.

Identifying the patients who are most likely to have durable responses to ICIs is key to guiding treatment decisions and is an area of active investigation. Researchers are trying to understand how the cellular and molecular characteristics of a patient's tumor as well as the patient's immune system can predict how well ICIs inhibitors will work (553,554). As one example, research has revealed that the extracellular matrix surrounding tumors that has high levels of a supportive molecule called collagen could predict how well a patient would respond to ICIs (555,556). Researchers are now trying to identify unique collagen biomarkers released into the blood to develop blood-based tests, which are less invasive and can be repeated over time to aid researchers and physicians in understanding the influence of extracellular matrix on patient response to cancer therapy and predict survival (557,558). Currently, researchers can detect fragments of collagen that are released during the production of extracellular matrix structures or during collagen degradation and remodeling (559-561).

CELL-BASED IMMUNE THERAPIES

Our increasing knowledge of the immune system and how it interacts with cancer cells is rapidly being harnessed to develop a type of immunotherapy called cell-based immunotherapy, which uses an immune cell as a therapeutic agent to attack cancer cells.

An approach that has already garnered a lot of attention is adoptive T-cell therapy, which has immense potential to boost the killing power of a type of immune cells called T cells (see sidebar on **What Is Adoptive T-Cell Therapy?**, p. 98). The goal is to dramatically increase the number of functional cancer-killing T cells in a patient. Six of these new types of immunotherapies, known as CAR T-cell therapies, have been approved by the FDA for treating patients with a range of blood cancers. Notably, some of the patients treated with these therapies during the first clinical trial in 2010 are still living cancer free (562,563).

CAR T-cell therapies involve collecting T cells directly from the blood of a patient with cancer and genetically altering them outside of the patient to target cancer cells. Unfortunately, the process for manufacturing CAR T cells is extremely time-consuming and resource intensive, which has led to long waiting lists for patients desperately seeking treatment (564). CAR T-cell therapy can also lead to several, sometimes life-threatening side effects including a phenomenon known as cytokine storm (565). Promisingly, many manufacturers and research groups have been able to streamline some parts of the manufacturing process and reduce the manufacturing time from the current standard of 16 days to about 48 or even 24 hours (566,567). However, other technologies are being developed to reduce the cost and amount of time it takes to produce these therapies.

A novel approach to CAR T-cell manufacturing that is being evaluated is to deliver the genetic modifications directly to T cells in a patient using nanoparticles (568), eliminating the most time-consuming aspects of the process—mainly, the isolation, shipping back and forth between manufacturing facilities, and reintroduction of cells into the patient, also called the "vein-to-vein" time. These nanoparticles can be available in the clinic on an as needed basis, reducing time to treatment initiation and quality control problems (569). Other upcoming technologies that are being tested include mixing T cells with the tools that genetically modify them to fight cancer into a type of sponge that can be implanted in the patient, which can be done in the clinic, eliminating shipping cells to the manufacturing facility (570).

Ongoing clinical trials are also testing immune cells from healthy donors that can be reprogrammed to be used in patients with cancer. In previous studies, using CAR T cells from another person led to rejection by the recipient because the donor cells were viewed by the patient's immune system as foreign. By using a different type of immune cells called natural killer (NK) cells, researchers have found a way to circumvent this problem (571,572). Another advantage of these so-called CAR NK cells is that they do not stay in the bloodstream as long as traditional CAR T cells, reducing the potential for long-term adverse effects such as development of autoimmune side effects, a common issue among immunotherapy recipients (573). Current clinical trials in several countries are exploring the use of these cells, which promise to overcome many of the challenges seen with CAR T-cell therapy (368).

Apart from CAR T-cell and CAR NK-cell therapies, another new cell-based therapy that is beginning to show promise in clinical trials uses a type of immune cells called tumor-infiltrating lymphocytes (TILs) that are derived from a patient's tumor. After the TILs are isolated from a tumor biopsy and expanded in numbers outside of the patient, they are reintroduced along with immune-stimulating agents into the patient.

TILs have advantages over other types of adoptive cell therapies because they are isolated directly from a tumor and do not need to be genetically manipulated. Because of this, they recognize multiple characteristics of the patient's tumor, which contrasts with CAR T cells that only recognize a single cancer-associated marker targeted by the engineered CAR.

TARGETING IMMUNOTHERAPIES DIRECTLY TO TUMORS

Several immunotherapies that treat cancer work by helping the body's immune system attack cancer cells; however, their use can have off-target effects that can damage healthy, noncancer cells, leading to debilitating side effects. New technologies are being tested that better target immunotherapies directly to the tumor, reducing the possibility of side effects. Researchers are experimenting with a device that is implanted near the tumor and releases molecules to recruit some immune cell types locally (574). This technology has been used successfully in animal models. Positive data from studies such as this provide rationale for movement into clinical testing. If this technology can be approved, this type of delivery method could help with other types of immunotherapies such as the previously described TILs by helping these cells more efficiently target the tumor from which they were originally isolated.

Controlling CAR T cells once they are in the body can increase their effectiveness by allowing them to home in on a tumor, rather than wasting time moving throughout the body or targeting other, non-cancerous cells and leading to side effects. To regulate CAR T cells, researchers are creating tools that activate these cells at the right time and place using either blue light or ultrasound radiation, which are focused more precisely on the tumor (575). Another research team is engineering these cells to be smarter by equipping them with a biological computer. These cells have cellular "circuits" that more specifically find cancer cells using multiple identification signals, drastically reducing off-target effects and toxicities (576).

TARGETING THE TUMOR IMMUNE MICROENVIRONMENT

To make the immune system more effective in eradicating cancer cells, manipulation of the tumor microenvironment is often necessary. This is because cellular and molecular components of the tumor microenvironment can lead to suppression of the antitumor immune system, preventing immunotherapies from working. One group of researchers utilized a nanoparticle delivery system to overcome this issue. The nanoparticles, which carry an inhibitor that promotes antitumor immune response, only release their cargo when they encounter the inhibitory molecules released by the tumor microenvironment. Once released, the inhibitor neutralizes factors that prevent the immune system from working and increases the response of tumors to immunotherapy (577). Overcoming the immune suppressive effects of the tumor microenvironment by using supplemental therapies such as these are essential to unleash the full power of immunotherapies.

mRNA CANCER VACCINES

The highly successful and rapid development and use of mRNA vaccines against the SARS-CoV-2 virus during the COVID-19 pandemic have reinvigorated interest in using mRNA vaccine platforms in the fight against cancers. In the same way that mRNA vaccines expose the immune system to parts of the virus so that it will subsequently recognize the virus during infection, cancer vaccines expose the immune system to part of a patient's tumor so the immune system can identify the tumor in the patient and eliminate it quickly and precisely. mRNA vaccines have already been used as a potential cancer therapeutic in several clinical trials over the past decade (578).

The technology developed for the COVID-19 vaccines, which includes using lipid nanoparticles to encase the mRNA or modifying the mRNA molecule itself to be more stable and evade the immune system, was originally developed for cancer vaccines. Now, researchers are using this technology in new clinical trials to improve cancer vaccines (579). To maximize the efficacy of the mRNA vaccine, current studies combine it with immunotherapies, helping to stimulate the immune system. The results are promising, with research groups already seeing success in patients (580).

Using Liquid Biopsies to Detect Cancers Earlier

Recent studies have demonstrated that it is possible to use blood or another biofluid sample, or "liquid biopsy," rather than a traditional tissue/tumor biopsy, to obtain material that can be analyzed to provide valuable information such as the molecular alterations associated with a patient's cancer (see **Moving Toward Minimally Invasive Cancer Testing**, p. 54). Liquid biopsies, therefore, provide a less invasive means to detect or track the status of cancer. There is much excitement in the cancer field that, as opposed to traditional biopsies which only provide a snapshot of the tumor characteristics at one specific time point, liquid biopsy approaches may generate a more complete picture of an individual's cancer by allowing for the monitoring of disease progression and its response to treatments in real time. While these tests have been approved for over a decade, starting in 2016 for detection of a mutation in the *EGFR* gene from plasma, they have increased their scope, with the ability to monitor cancer progression, detect genetic mutations, recognize signs of relapse, and even determine if a

patient will respond to certain types of therapies. The routine use of liquid biopsies will increase the accuracy of cancer diagnosis and treatment and increase efficiency compared to a traditional biopsy (581).

New evidence from an international clinical study demonstrated that measuring circulating DNA in the blood after surgery of tumors helped guide the future use of chemotherapy. By knowing if a patient was positive for circulating tumor DNA (ctDNA) after surgery, which indicates the possible presence of cancer cells, researchers would be better informed regarding administration of chemotherapy. The study demonstrated that using this type of approach led to reduced use of chemotherapy overall and improved patient outcomes without compromising recurrence-free survival (582).

Liquid biopsy approaches are also becoming more precise. By using ctDNA from blood, researchers can not only detect the presence of a tumor but also determine the potential prognosis of that cancer or if it has the potential to progress (583,584). This is done by looking at several different types of ctDNA that are released by a tumor over time since the pattern changes as the tumor evolves. One study looked at ctDNA found in urine and blood of children with either stage III or IV Wilms tumor, one of the most common kidney cancers in children. This study detected the mutations present in the ctDNA and compared them to the mutations found in a biopsy from the tumor itself. The researchers found that the mutations were able to be accurately detected in the ctDNA and that these mutations were useful as prognostic markers for these types of tumors (583). Collectively, these data demonstrate how safer, less invasive biopsies such as using ctDNA from blood can potentially transform clinical cancer care in the future (583).

On the other hand, screening healthy individuals for cancers may lead to either over- or underdiagnosis of cancers, which makes some physicians and scientists question the capabilities of liquid biopsy tests. To determine their effectiveness in detecting cancers compared to standard surveillance methods such as mammograms, NCI advisors have endorsed a four-year pilot study that will enroll 24,000 people to assess liquid biopsy tests produced from several commercial companies starting in the year 2023 (585).

Impacting the Future of Cancer Research and Patient Care Through Evidence-Based Policies

IN THIS SECTION YOU WILL LEARN:

- Continued funding for NIH and NCI is vital to accelerate the pace of new scientific breakthroughs against cancer and build programs focused on the training and retention of a diverse cancer research workforce.
- Federal policy advancements from FDA, CDC, and NCI improve diversity and access to clinical trials, access to cancer screening, and cancer outcomes.
- Disparities in the cancer burden must be addressed through equitable access to health care, insurance, optimal nutrition, and physical activity.
- Public health resources are essential for understanding the impact of cancer health disparities, and these systems need additional investment to truly support the communities they serve.

Investments and policies enacted by Congress and programs implemented by federal agencies including NIH, NCI, CDC, and FDA are essential to making progress against the collection of diseases we know as cancer.

The 21st Century Cures Act, which was signed into law in December 2016, authorized $1.8 billion to fund the Cancer Moonshot, an initiative led by NCI with the goal of accelerating the pace of progress against cancer through prevention, screening, scientific discovery, collaboration, and data sharing, over a seven-year period. Congress has continued to appropriate full funding for the Cancer Moonshot (see sidebar on **The Cancer Moonshot**, p. 126).

The 21st Century Cures Act also established the FDA's Oncology Center of Excellence (OCE). OCE was established to support the development of anticancer therapies with an emphasis on facilitating active collaboration between OCE and other FDA centers. These efforts have focused on diversifying and decentralizing clinical trials to improve minority representation when developing new therapeutic options with the goal of achieving patient-centered regulatory decision making through innovation and collaboration. OCE plays a crucial role in reviewing new breakthrough treatments to ensure they are safe and effective for patients with cancer.

In February 2022, President Joseph R. Biden, Jr., announced a reignited Cancer Moonshot with a mission to "reduce the death rate from cancer by at least 50 percent over the next 25 years and to improve the experience of people and their families living with and surviving cancer—and, by doing this and more, end cancer as we know it today." The Cancer Moonshot, along with many other cancer-based initiatives, marks the continued commitment of Congress and the Executive Branch to cancer research and improving patient outcomes. To realize the goals of the reignited Cancer Moonshot, the full reach of the federal government, including NIH, NCI, FDA, and CDC, will be utilized to better prevent, detect, and treat cancer.

The Biden administration has also proposed the creation of an Advanced Research Projects Agency for Health (ARPA-H), designed to prioritize high-risk, high-reward approaches to prevent, diagnose, and cure diseases such as cancer. In the Fiscal Year (FY) 2022 funding bill, ARPA-H received $1 billion in start-up capital to begin creation of this new medical research authority, which is proposed to be housed within NIH. As Congress continues to debate the structure and location of ARPA-H, it is imperative that funding for ARPA-H supplement, and not supplant, funding for NIH's core research functions.

The CDC's Division of Cancer Prevention and Control (DCPC) is another important federal partner in fueling progress against cancer. DCPC brings science-driven public health interventions, including cancer screening and prevention programs, to communities across the country. DCPC works with state health agencies, territories, tribes and tribal organizations, and other key organizations to develop, implement, and promote effective cancer prevention and control practices.

President Biden's vision of ending cancer as we know it will not be realized without robust, sustained, and predictable funding for basic research. Significant annual funding increases are essential for NIH, NCI, FDA, CDC, and other agencies to continue their vital work against cancer. Meanwhile, legislation aimed at increasing and diversifying participation in clinical

The Cancer Moonshot

In January 2016, the Obama Administration announced the Cancer Moonshot, an ambitious endeavor to accelerate progress against cancer. Congress passed the 21st Century Cures Act in December 2016, authorizing $1.8 billion in funding for the Cancer Moonshot over seven years. To date, Congress has appropriated over $1.5 billion in Cancer Moonshot funding, which has supported a wide range of cancer research initiatives to accelerate discovery, increase collaboration, reduce cancer health disparities, and expand data sharing. Since 2017, NCI initiatives under the Cancer Moonshot have resulted in nearly 250 projects across a broad range of urgent cancer needs. These projects are delivering important insights into the mechanisms that drive cancer and point to areas where we can intervene and they have also identified several candidates for new approaches to prevent, detect and treat cancer.

The Cancer Moonshot brought together a large community of people with cancer, patient advocates, investigators, and clinicians who are dedicated to accelerating cancer research to improve the lives of people with cancer and their loved ones. Below are Cancer Moonshot featured projects from 2017-2022 that highlight the progress of Moonshot efforts:

Accelerating childhood cancer treatments with fewer long-term and late effects. Developing new treatment approaches for childhood cancers driven by fusion oncoproteins.

Addressing disparities in colorectal cancer screening among American Indians, using a patient navigation program including community, clinician, and patient input.

Prioritizing diversity, equity, and inclusion in genomics research by engaging cancer patients and survivors from diverse backgrounds to address knowledge gaps in understanding genomic changes in tumors.

Enhancing immuno-oncology research significantly, including developing early-stage preclinical immunotherapy approaches, including CAR T cell antibodies, to treat pediatric cancers and identify biomarkers of immunotherapy resistance.

Supporting data sharing tools and services through the Cancer Research Data Commons to learn from every patient.

Establishing a network of researchers focused on preventing, mitigating, and addressing adverse physical and psychosocial effects in survivors of pediatric and adolescent/young adult (AYA) cancers.

Testing if a single dose of the Human Papillomavirus (HPV) vaccine can increase the prevention of cervical cancer, particularly where cost and logistics of the multiple-dose schedule have impeded vaccination uptake.

Generating dynamic 3D human tumor atlases to help researchers and physicians "see" a tumor and broadly sharing the atlases, data, and computational tools through the Human Tumor Atlas Network Data Portal.

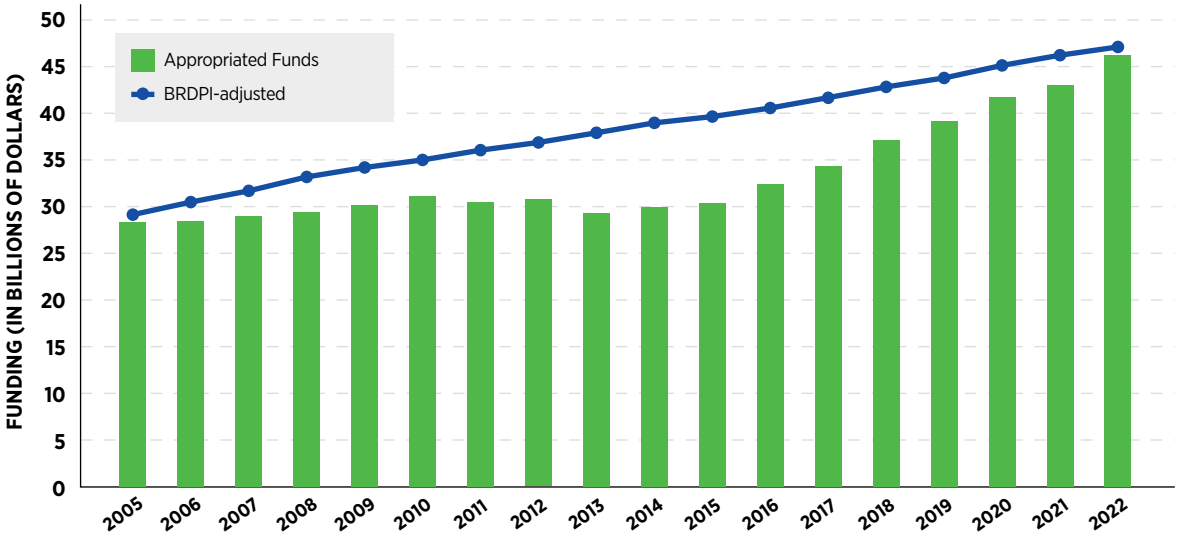
For more information and updates, visit **cancer.gov/moonshot**, which includes progress under each recommendation, a series of seminars, and a page and video series dedicated to progress.

In February 2022, President Biden announced that his administration is reinvigorating the Cancer Moonshot. The next phase of the Cancer Moonshot has two ambitious goals: Cut the death rate from cancer by 50 percent and improve the lives of people and their families living with and surviving cancer. Taken together, these actions will help end cancer as we know it.

As the cancer research arm of the federal government, NCI is uniquely qualified to lead the next phase of Cancer Moonshot research. Through several new or enhanced research programs that will fall under the reinvigorated Cancer Moonshot, NCI and the cancer research community will work together to improve cancer detection methods and enable greater uptake of proven approaches to prevent and treat cancers of all types among all communities. By collaborating across government and the private sector and by working with people with cancer and the advocacy community, we can achieve the President's goal of "ending cancer as we know it."

FIGURE 13

NIH Funding: Continuing the Momentum of Robust Increases



NIH appropriations from 2005 to 2022 are steadily closing the gap between appropriated funds and projected costs to conduct research, as illustrated by Biomedical Research and Development Price Index (BRDPI), shown in blue. Continued bipartisan efforts are urgently needed to close this gap and ensure a continued investment in lifesaving cancer research.

Data from https://officeofbudget.od.nih.gov/pdfs/FY22/gbipricesindexes/BRDPI_Proj_March_2022_Final.pdf.

trials; expanding access to quality, affordable health care; and accelerating progress against pediatric cancers will be vital to reducing cancer disparities and achieving health equity. In addition, investments in access to preventive care, reduction of tobacco-related illness through strong federal regulations, and access to healthy lifetime nutrition are some of the ways in which we can decrease cancer incidence and improve outcomes.

Investments in Research Fuel a Healthier Future

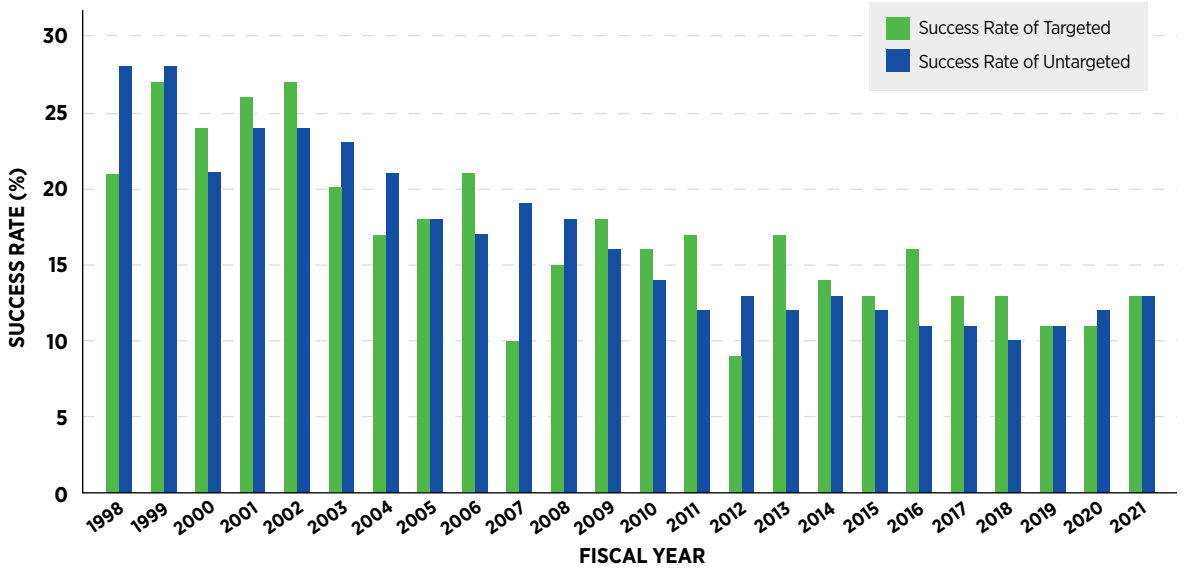
Remarkable advances in medical research have led to significant improvements in cancer prevention and reductions in cancer mortality. In the years since the enactment of the National Cancer Act in 1971, cancer mortality has dropped by 27 percent (3). This progress is a result of NCI investments in research that developed state-of-the-art anticancer therapies and more effective screening tools to detect cancers in earlier stages, as well as initiatives through CDC to raise awareness of cancer prevention and the importance of cancer screenings. As a result of these efforts, there are now more than 18 million cancer survivors living in the United States (2).

To continue progress against cancer, significant federal investments will be needed. Beginning in FY 2005, a decade of stalled funding at NIH caused budgets to be eroded by inflation. As a result, NIH's purchasing power—the amount each dollar invested can buy—was reduced by nearly 25 percent compared to the previous decade (586). This had a devastating impact on the ability of NIH to adequately fund research. Thanks to strong bipartisan support, Congress has made investments in medical research a top priority, increasing NIH funding by $14.9 billion over the last seven fiscal years, an increase of roughly 49 percent since FY 2015 (see **Figure 13**, p. 127).

In FY 2022 alone, congressional leaders provided an increase of $2.25 billion for NIH and an increase of $353 million for NCI. As a result, NIH's funding for medical research has almost returned to the capacity last seen in FY 2005, as measured by the Biomedical Research and Development Price Index (BRDPI) (see **Figure 13**, p. 127). In particular, Chair Rosa DeLauro (D-CT), Ranking Member Tom Cole (R-OK), Chair Patty Murray (D-WA), and Ranking Member Roy Blunt (R-MO) have demonstrated remarkable leadership and commitment to medical research in their roles on the Labor, Health and Human Services, Education, and Related Agencies Appropriations Subcommittees in the House and Senate, respectively.

FIGURE 14

NCI Success Rates



Success rates at NCI, i.e., the percentage of grant applications that receive funding through NCI, have steadily declined over the past two decades for both targeted and untargeted research. Targeted research is the research for which an institute solicits grant applications in a specific scientific area using Request for Applications (RFAs), and funds meritorious applications from a pool of dollar amount specifically set aside for that research area. Untargeted Research is the research that is not funded through grant solicitation in response to an RFA.

Data from https://report.nih.gov/nihdatabook/report/157.

NIH funding increases also benefited NCI, which received an increase of $1.96 billion over the last seven fiscal years, to $6.912 billion, an increase of nearly 40 percent. With these funds, NCI provides support through a competitive process to research grants that can cover anything from basic laboratory science to clinical research. Unfortunately, despite seven consecutive years of bipartisan congressional support for investments in medical research, NCI still faces significant funding pressures that limit the amount of support it can provide for meritorious investigator-initiated research.

The percentage of approved research grant applications that receive funding are referred to as the success rate. In 1999, success rates reached 32 percent across NIH and 28 percent at NCI. These generous levels of funded grants fueled cancer discoveries at unprecedented rates and contributed to the advances in cancer care that we benefit from today (587). However, NCI funding has not kept pace with the subsequent exponential growth of applications. Between 2013 and 2018, NCI received a nearly 46 percent increase in grant applications, overshadowing the increase of other institutes at NIH which only increased by 4.9 percent.

Despite the funding provided by Congress, NCI's success rate in FY 2021 was only 13 percent, less than half the rate of two decades ago (587) (see **Figure 14**, p. 128). NCI's success rate is also among the lowest of all institutes at NIH. Currently, fewer than one in seven approved grant applications is funded, leaving well-reviewed science unfunded and jeopardizing the United States' position as a global leader in cancer research. In addition, lack of funding can potentially have far-reaching consequences for the cancer research community and the ability to recruit, train, and retain the next generation of cancer scientists. These trends can result in fewer women and underrepresented minorities (URMs) choosing careers in Science, Technology, Engineering, Mathematics, and Medicine (STEMM). By meeting the NCI Director's Professional Judgment Budget level of $7.766 billion in FY 2023, NCI can increase the availability of research grants and accelerate the path to discoveries that will save lives.

CDC's Division of Cancer Prevention and Control (DCPC) works with state and local governments, community organizations, and health providers to promote cancer prevention and early detection. These collaborations include funding for central cancer registries; comprehensive cancer control, which includes state, tribal, local, and territorial organization cancer planning; the National Breast and Cervical Cancer Early Detection Program; and initiatives focused on

colorectal, skin, prostate, and ovarian cancer, as well as HPV-associated cancers.

Despite the importance of these public health-related programs, increased investments in CDC's DCPC have also been minimal. Between FY 2010 and FY 2022, funding for these vital initiatives increased by a total of $8 million, or just 2.9 percent. This amounts to an estimated $100 million deficit relative to what the funding would be if adjusted for inflation from FY 2010 (588). As more than 40 percent of cancer cases in the United States each year are linked to modifiable risk factors and can be prevented, these initiatives and collaborations are critical to reduce the cancer burden.

Congress has made a clear and decisive commitment to medical research over the last seven fiscal years, returning NIH to a trajectory of steady funding growth. However, more must be done to expand opportunities in medical research, cancer prevention, and cancer treatment. With so many scientific opportunities to make progress against cancer and other diseases, it is imperative that our elected leaders continue to provide robust, sustained, and predictable increases in funding for medical research and cancer prevention at NIH, NCI, CDC, and FDA.

Building a Diverse Cancer Research Workforce Drives Innovation

To prevent and cure all cancers, the next generation of cancer researchers will require thoughtful education, training, and support throughout their career paths. To realize the full potential of our medical research enterprise, research institutions must be proactive in recruiting, supporting, and retaining a cancer research workforce that reflects the diversity of our society. As described in the *AACR Cancer Disparities Progress Report 2022*, the amount of diversity within the cancer research workforce lags behind that of the general U.S. population. Also, complex, interrelated factors contribute to the low rates of URMs in STEMM. Proposed methods to overcome cancer disparities include increasing diversity early and consistently throughout the cancer research and care workforce. Furthermore, additional training in mentorship for successful senior scientists helps support the professional development of their trainees. Formal training programs, incentives, and compensation for excellence in mentorship have been shown to increase retention of URM trainees and scientists. NIH and NCI play important roles in fostering development of young researchers into becoming the scientific and clinical leaders of the future.

Encouraging early childhood interest in STEMM improves the likelihood of earning a higher degree (589). NIH sponsors the Science, Education, Partnership Awards (SEPA) Program, which facilitates partnerships between medical and clinical researchers, preK-12th grade teachers, schools, and other educational organizations (590). For example, the SEPA-sponsored high school program at the University of Arizona, Q-Cubed, has been instrumental to increasing the percentage of high school students that attend college. Since the launch of Q-Cubed, 98 percent of the program participants either attended or graduated from two- to four-year colleges (591). These programs and awards provide valuable early exposures to the world of medical research and showcase the benefits of a career in research.

The NCI Center to Reduce Cancer Health Disparities provides funding support for URMs beginning in middle school and continuing to junior tenure-track faculty positions through the Continuing Umbrella of Research Experiences (CURE) program. Between 2001 and 2012, CURE supported more than 3,000 early-career researchers, who generated greater than 1,700 peer-reviewed publications (592). In addition, the Intramural Continuing Umbrella of Research Experiences (iCURE) program brings undergraduate students, post-baccalaureate and post-master's degree individuals, graduate students, and postdoctoral fellows into the NCI research community and supports mentored research experiences. iCURE particularly encourages the participation of individuals from underrepresented populations and aims to further NCI's interest in increasing diversity in cancer research workforce.

Within the cancer research and care workforce, early-career researchers are instrumental in making advances against cancers as they bring innovative ideas and highly original perspectives to their research projects. Graduate students and postdoctoral fellows are the largest share of the academic research workforce. Trainees can be supported under their advisors' grants, competitive institutional "T" awards, or individual "F" and "K" awards, as well as competitive philanthropic awards. These awards cover stipend and research costs of promising pre- and postdoctoral scientists, which enables them to take on more ambitious research. Some of these awards are focused on trainees that are URM in STEMM, while others, like the K99/R00 award, are designed to transition postdoctoral researchers into independent investigator positions. NCI and NIH have created several funding mechanisms to directly support URM early-stage investigators (ESIs). For example, the K01, K99/R00, and R21 grant mechanisms support the transition of postdoctoral early-career scientists into becoming independent researchers and some K01 and R21 grants are focused on supporting URM scientists (593, 594). Additionally, NIH Institutes and Centers issued 171 student loan repayment awards in FY 2020 totaling almost $13 million for investigators involved in health disparities research (595). Focused approaches to funding ESIs, and women researchers identifying as URMs, should be a priority, as this could improve recruitment and retention within the cancer research workforce (see sidebar on **NIH and NCI Initiatives to Promote Workforce Diversity and Outreach**, p. 130).

NCI has also taken steps to support junior tenure-track research faculty. For example, NCI has helped ESI applicants establish independent laboratories by extending R01 paylines to the 16th percentile, instead of the standard 11th percentile (596). Additionally, ESI R01 applications within the 11th percentile are eligible for the R37 Method to Extend Research in Time (MERIT) award, which provides funding for up to seven years instead of the traditional five years (597). The additional time provided by R37 MERIT awards enables further data

NIH and NCI Initiatives to Promote Workforce Diversity and Outreach

NCI EQUITY AND INCLUSION PROGRAM (EIP)

The EIP, which is overseen by the NCI Equity Council and five working groups, strives to:

- Increase the diversity of the cancer research workforce.
- Build a more equitable and inclusive NCI community.
- Address cancer disparities and advance health equity.

CONNECTING UNDERREPRESENTED POPULATIONS TO CLINICAL TRIALS (CUSP2CT)

The CUSP2CT program implements and evaluates multilevel and culturally tailored outreach and education interventions with the primary goal of increasing referral and, ultimately, the accrual of underrepresented racial and ethnic minority populations to NCI-supported clinical trials. CUSP2CT will address cancer health disparities through a network of local multidisciplinary and integrated partners that includes community health educators, lay health advisors, community members, health care providers, and researchers working in coordination to educate and refer racial and ethnic minority populations to NCI-supported clinical trials and increase provider awareness about racial and ethnic minority participation in NCI clinical trials.

EARLY INVESTIGATOR ADVANCEMENT PROGRAM (EIAP)

With the support of its Equity Council, in December 2021, NCI launched EIAP to facilitate the advancement of scientists from diverse backgrounds to become independent investigators.

The cancer research enterprise needs a continuous flow of talent through the research career pipeline. One critical juncture is the transition from junior investigator to independent investigator. EIAP aims to enhance professional skills, guide preparation of an R01 grant application, provide access to a mentoring and peer network, and grow a community of emerging independent investigators from diverse backgrounds.

Each year, EIAP will support the professional and career development of a cohort of eligible and qualified early-stage investigators (ESIs) and new investigators from institutions across the country. Cohort members will provide peer support for each other, both during and beyond their participation in the program.

FACULTY INSTITUTIONAL RECRUITMENT FOR SUSTAINABLE TRANSFORMATION (FIRST)

NIH launched the FIRST program with the goal of developing cultures of inclusive excellence—scientific environments that can cultivate and benefit from a full range of talents—at NIH-funded institutions. Inclusive excellence hinges on enhancing diversity and inclusion, as well as institutional culture change. Fostering inclusive environments that cultivate and benefit from a full range of talents is not only essential for the quality and impact of science, but it also improves stewardship of federal funds to ensure that the most talented researchers are recruited, supported, and advanced to become competitive research investigators.

PROFESSIONAL ADVANCEMENT VIRTUAL ENGAGEMENT SERIES (PAVES)

Launched during the pandemic, this seminar series hosted by the Center to Reduce Cancer Health Disparities (CRCHD) is held monthly and offers professional development for both intramural and extramural grantees and trainees. From networking to learning about cancer systems biology or transitioning to faculty positions, the experiences and information are fruitful.

TRAINING NAVIGATION

CRCHD uses a Training Navigation model to facilitate and increase the successful entry of underrepresented scholars into the **Continuing Umbrella of Research Experiences (CURE)** training pipeline and to transition existing CURE scholars through the CURE pipeline to career independence. Training Navigation also aims to provide career development support for the advancement of early- to mid-career and tenured investigators to develop the skills necessary to obtain R-type funding and achieve career advancement.

The Training Navigation model has also been leveraged by the **Geographic Management of Cancer Health Disparities Program (GMaP)**. GMaP is a national program designed to enhance the recruitment and career/professional development of underrepresented investigators, trainees, and students; communication and dissemination; and evaluation, as part of building region-based "hubs" for the support and efficient management of cancer health disparities research, training, and outreach. GMaP-supported activities include addressing questions from potential applicants and GMaP Regional Coordinating Directors, performing NCI outreach activities, promoting new and existing funding opportunities, hosting/supporting webinars and workshops, connecting scholars with potential mentors and regional training opportunities, and identifying existing NIH career development/grantsmanship resources and available tools. Tracking investigators as they mature is important to monitor for career progression and growth.

YOUTH ENJOY SCIENCE (YES) RESEARCH EDUCATION PROGRAM

The NCI YES program facilitates the education of students from diverse backgrounds underrepresented in medical research who will become knowledgeable about cancer, and available to focus on cancer later in their careers. The program will support efforts to create and maintain institutional programs that engage grades 6-12 and/or undergraduate students from underrepresented populations in cutting-edge cancer research experiences. These efforts will enhance the pool of individuals from underrepresented backgrounds interested in pursuing a career in medical research via early intervention strategies. Proposed institutional programs may also provide research experiences for the grade 6-12 teachers and undergraduate faculty members who serve underrepresented student populations. The specific goals are to inspire interest in medical sciences, help envision research as a career path, and strengthen practical research and career skills. In alignment with these goals, institutions may develop unique programs that capitalize on their research strengths and are responsive to their target populations.

Adapted from (8).

collection for a second grant application and also supports the awardee through the tenure process, which lasts approximately seven years.

The influx of innovative ideas from young scientists continues to be critical for future breakthroughs against cancer and other deadly diseases. As Congress considers appropriations for NIH and NCI, it will be vital to invest in additional resources to support early-career researchers. Robust, sustained, and predictable funding increases for NIH and NCI are critical to ensure that these programs continue.

Improving Regulatory Science to Ensure Safety and Efficacy of Cancer Therapies

Regulatory review by FDA ensures medical research delivers safe and effective anticancer therapies for patients. To provide efficient oversight, FDA's processes, staff, and technology must keep pace with the rapid advances in new target discovery and drug development to treat cancer. User fees paid by the industry when submitting applications and congressionally appropriated funds are both essential sources of support to FDA's mission. Investments from Congress support critical regulatory science programs that help improve the regulatory process and shorten the time it takes for new advances in medicine to reach patients in need.

As one example, FDA OCE was established in 2017 by the 21st Century Cures Act to support development of anticancer therapies and improve regulatory efficiency in oncology. OCE facilitates collaborations between staff members with oncology expertise from other FDA centers, including the Center for Drug Evaluation and Research, Center for Biologics Evaluation, and Center for Devices and Radiological Health.

DIVERSIFYING AND DECENTRALIZING CLINICAL TRIALS

The types of cancer included in clinical trials see the greatest advances in treatment and survival (598,599). Clinical trial participants often experience better clinical outcomes compared to nonparticipants (600). On average, 55 percent of adult patients with cancer join a trial when asked (601). Unfortunately, overall participation in clinical trials is very low; only 8 percent of adult patients and 19.9 percent of pediatric and adolescent patients with cancer participate in clinical trials in the United States (602,603). While academic medical centers tend to have above average trial participation rates (602), most patients with cancer are seen at community clinics or hospitals where trials are less prevalent. Another key reason for low trial participation is that more than 75 percent of patients with cancer either do not have a trial available for their specific disease or the strict eligibility criteria exclude them because of comorbidities or prior treatments (602). Additional challenges for clinical trials include communities without any health care facilities, patients not being asked to join a trial, lack of trust in medical research, dependent care needs, and costs and time related to participation (604-606). These challenges disproportionately impact racial and ethnic minorities, contributing to disparities in clinical trial participation rates.

The **Diverse and Equitable Participation in Clinical Trials (DEPICT) Act** (H.R. 6584) would grant FDA new authorities to ensure clinical trial participants reflect real-world patient populations by **increasing representation of racial and ethnic minorities**.

The **Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act** (H.R. 5030/S. 2706) would **increase support for decentralized clinical trials** and address challenges for trial participation by allowing travel expense reimbursement and supporting telehealth and remote monitoring.

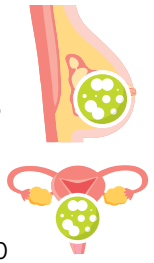
Improving representation of racial and ethnic minorities in oncology clinical trials is a key priority of OCE. In April 2022, OCE released draft voluntary guidance on creating prospective diversity action plans when submitting Investigational New Drug or marketing applications (607).

Voluntary FDA guidance is an important first step to improving clinical trial participation and representation. Additional authority to issue and enforce requirements in clinical trials could greatly enhance positive changes to the drug development process. The Diverse and Equitable Participation in Clinical Trials (DEPICT, H.R. 6584) Act would help accomplish these goals by allowing FDA to require diverse representation (608). The Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act (H.R. 5030/S. 2706) would also support greater trial participation by allowing trial sponsors to reimburse patients for transportation costs and increasing the use of telemedicine and remote data collection (609). Furthermore, engaging patients and other stakeholders is critical to identify creative solutions in the policy making process and build trust in medical research.

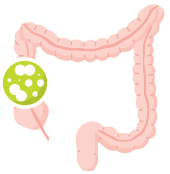
Improving Anticancer Therapy Access for Older Adults

FDA is also working to improve trial access and outcomes for patients with cancer older than 65 years old. These patients represent more than half of all patients with cancer (610), but are often excluded from clinical trials due to explicit age eligibility criteria or exclusion criteria for having other medical conditions or taking medications. As a result, oncology clinical

CDC and NCI Cancer Screening Programs



Since its inception in 1991, CDC's **National Breast and Cervical Cancer Early Detection Program** has helped low-income, uninsured, and underinsured women gain access to cancer screening, diagnostic, and treatment services. In 2020, the program provided breast cancer screening to 227,000 women, diagnosing about 2,300 invasive breast cancers and 600 premalignant lesions before they turned into cancer. The program also provided cervical cancer screening to nearly 99,000 women, diagnosing around 110 invasive cancers and 5,700 premalignant lesions.



The CDC **Colorectal Cancer Control Program** was established in 2015 to increase colorectal cancer screening rates. It currently includes 831 clinics that serve 1.3 million patients ages 50 to 75, including many uninsured patients. Clinics that have participated since the program's inception have increased screening rates by 12.3 percent.

The NCI **Screen to Save: National Colorectal Cancer Outreach** initiative aims to increase awareness and knowledge about colorectal cancer screening and screening rates among racially and ethnically diverse and rural communities through community health educator-conducted community outreach and education.

trials include patients that are on average 6.49 years younger than the patient population affected (611).

FDA's Project Silver is a global regulatory effort to highlight drug development programs with indications particularly impacting patients 65 years old and older. This public health initiative promotes increased enrollment of geriatric patients in clinical trials for anticancer therapeutics (612). As part of Project Silver, FDA issued final voluntary guidance in March 2022 to encourage trial sponsors to broaden the age range to increase the number of participants over the age of 65 in oncology clinical trials (613). The guidance emphasizes the importance of including older adult patients in early phase trials to analyze safety with co-morbid conditions and other medications. Another key recommendation was to add older adult patients to standard randomized clinical trials as an additional trial arm. This would allow trial sponsors to keep primary endpoints focused on outcomes of younger adult patients, and secondary endpoints could include data from older adult patients while expanding access to investigational therapies.

Congress recently enacted legislation intended to benefit older adults, including those with cancer, who receive health coverage under Medicare. This new law limits the out-of-pocket amount that a Medicare beneficiary would pay for prescription drugs to $2,000 per year beginning in 2025. It also allows the federal government to negotiate the price of some high-cost prescription drugs with manufacturers. Together, these policies are intended to reduce the cost of prescription drugs and make lifesaving treatments and more accessible and affordable.

Advancing Policy to Strengthen Cancer Prevention and Screening Programs

Preventable risk factors, including tobacco use, infections, and UV exposure, account for approximately 40 percent of cancer cases in the United States (see **Preventing Cancer: Identifying Risk Factors**, p. 28). Detecting cancer early through routine screenings for common cancers also greatly improves treatment options and outcomes (see **Screening for Early Detection**, p. 46). Inequities in access to cancer screenings and follow-up treatment are major contributors to late-stage diagnoses among underinsured and uninsured patients. CDC's National Breast and Cervical Cancer Early Detection Program and Colorectal Cancer Control Program help provide underserved patients with routine cancer screenings (see sidebar on **CDC and NCI Cancer Screening Programs**, p. 132). Unfortunately, limited funds result in continuing gaps in access to cancer screenings (614). Additional federal investment for these programs would improve equity in cancer screening and follow-up care. Growing evidence suggests expanding Medicaid has resulted in early detection of breast cancers (615); thus, Medicaid expansion is another substantive approach to achieving health equity.

HPV infections can lead to six types of cancer, including nearly every case of cervical cancer (see **Prevent and Eliminate Infection with Cancer-causing Pathogens**, p. 38) (616). Guideline-concordant HPV vaccination, cervical cancer screenings, and timely follow-up care are effective strategies to prevent cancer and potentially eliminate all cases of cervical cancer. However, uptake of HPV vaccination has been suboptimal; among eligible U.S. teens in 2020, less than 60 percent were fully vaccinated against HPV (194). State-level policies requiring vaccines for other diseases, such as measles, have been particularly effective at nearly eradicating the viruses that cause them. However, only Hawaii, Rhode Island, Virginia, Puerto Rico, and Washington, DC, require HPV vaccination for attending public school (617). Eliminating HPV-related cancers will only be achieved by coordinated strategies among all stakeholders to build confidence in vaccination and improve screening and treatment for HPV-related lesions.

LEVERAGING POLICY TO REDUCE TOBACCO-RELATED ILLNESS

Smoking rates among U.S. adults are at a historic low following decades of awareness campaigns and effective tobacco control policies. Adult smoking rates peaked in the 1960s when nearly half of adults smoked. In 2020, 19 percent of U.S. adults regularly used any tobacco product (87), and only 12.5 percent of adults regularly smoked cigarettes. Concerningly, tobacco use remained higher among U.S. youth in 2020, including 23.6 percent of high school students who used tobacco products, primarily flavored e-cigarettes (618,619). The ongoing epidemic of youth nicotine addiction threatens to reverse progress made against tobacco-related disease. Additional tobacco control policies across all levels of government remain important to continue reducing tobacco-related cancers as smoking remains the number one preventable cause of cancer.

In April 2022, FDA unveiled two proposals that would prohibit menthol cigarettes, as well as all flavored cigars (620,621). These proposals were welcomed by public health organizations, including AACR, that have advocated for a menthol cigarette ban for nearly 10 years. A large body of evidence, including studies from the tobacco industry, demonstrates that menthol increases smoking initiation, nicotine exposure, and the difficulty of tobacco use cessation (622) (see **Figure 15**, p. 134). Decades of predatory advertising practices for menthol cigarettes in predominantly racial and ethnic minority communities are responsible for large tobacco-related health disparities (623).

Additionally, FDA also announced in June 2022 that it would pursue a new proposal to limit the amount of nicotine in combustible tobacco products (625). This rule is estimated to prevent eight million tobacco-related deaths during the next 80 years (626). If finalized, this could be one of the most powerful regulations ever implemented by FDA to protect public health.

In an effort to address the negative public health impacts of e-cigarettes, especially among youth, FDA deemed e-cigarettes to be classified as tobacco products and therefore under FDA's authority. Following this classification, manufacturers were required to submit premarket tobacco product applications (PMTAs) for e-cigarettes to FDA for regulatory review. The Family Smoking Prevention and Tobacco Control Act places the responsibility on the manufacturers to provide scientific evidence within PMTAs proving that their products are appropriate for the protection of public health. More than 6.6 million PMTAs were submitted to FDA by the September 2020 deadline (627). FDA has since reached decisions on 99 percent of the submitted products, and almost all were denied marketing orders. In 2022, FDA reached decisions on several e-cigarette brands with large market shares. While FDA authorized several VUSE and NJOY branded e-cigarettes, they decided to remove JUUL-branded e-cigarettes from the market, pending an appeal (628). JUUL e-cigarettes comprised approximately 75 percent of the e-cigarette market in 2019 and were a major contributor to a doubling of the youth e-cigarette use between 2017 and 2019 (629,630). JUUL's intentional marketing to youth and addicting millions to nicotine demonstrate that its products are not appropriate for public health.

BANNING MENTHOL CIGARETTES **WOULD SAVE 650,000 LIVES** BY 2060 (624)

Further policies that could reduce tobacco-related illness include expanding flavor prohibitions to all tobacco products; increasing restrictions on tobacco product advertising and promotions; and increasing funding for awareness and cessation programs within FDA, NCI, and CDC's Office on Smoking and Health.

Accelerating Progress Against Pediatric Cancers

Pediatric cancers are the leading cause of disease-related deaths in children up to the age of 14 years (1). Advances in cancer treatments over the last few decades have resulted in an increase in survival rates for pediatric cancer to 85 percent (1). However, there are many types of pediatric cancers with significantly poorer outcomes and for which there are no effective treatments. Additionally, children who survive cancer face long-term side effects from their treatment, as well as life-threatening late effects of childhood cancer (see **Challenges Faced by Cancer Survivors**, p. 102). It is imperative to develop policies that support identifying new treatments for pediatric cancers and advocate for survivors of childhood cancers. This is critical to ensuring the best outcome for every child impacted by cancer. The most comprehensive childhood cancer legislation to date was passed by Congress in 2018, the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act. Congress has consistently appropriated $30 million per year to fund programs created by the STAR Act. Numerous provisions within the STAR Act have been implemented to improve data collection, tracking, and survivorship support related to childhood cancers, such as:

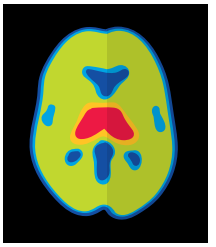
- Awarding NCI grants to support and expand the collection of biospecimens from children, adolescents, and young adults diagnosed with cancer;
- Expanding childhood cancer surveillance programs at CDC by developing a new cloud-based data reporting system;
- Supporting research that will investigate the late effects of pediatric cancer treatments, improve collaboration among health care providers, and identify novel methods of care for pediatric cancer survivors; and
- Mandating the inclusion of at least one pediatric oncologist on the National Cancer Advisory Board.

Continued full appropriations will be essential to realizing the potential of the STAR Act. The Childhood STAR

FIGURE 15

How Flavored Tobacco Products Contribute to Disparities

Masks Harsh Taste

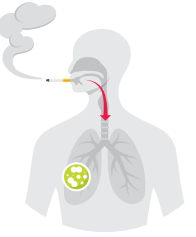


Menthol Increases Nicotine Receptors

Youth More Likely to Try

Cooling Effect of Menthol Hides Smoke Irritation

Predatory Marketing



Tobacco Smoke Causes 17 Types of Cancer Beyond Lung

The tobacco industry has used flavored products and predatory marketing practices, such as providing free samples of menthol cigarettes, to addict racial and ethnic minority communities to nicotine for decades. These aggressive campaigns were intentional business strategies to preserve market share as overall smoking rates dropped across the United States.

Reauthorization Act (H.R. 7630/S. 4120) was introduced in the House and the Senate in April 2022. Congress will need to reauthorize the STAR Act before its expiration at the end of FY 2023 to continue NCI-supported research and further development of biorepositories, identify and train pediatric cancer researchers, and strengthen infrastructure to capture pediatric cancer incidences.

The Childhood Cancer Data Initiative (CCDI) is another NCI program designed to improve data collection and research sharing related to pediatric cancers. The goals are to better understand cancer biology specific to children and to improve prevention, treatment, quality of life, and survivorship. CCDI funding is proposed for 10 years, from FY 2020 to FY 2029, with $50 million to be allocated each year. Congress fully funded the initiative in both FY 2020 and FY 2021. NCI has granted CCDI funds for pediatric cancers and research activities and has also engaged the entire childhood cancer community in the implementation of the initiative. In March 2022, the CCDI Molecular Characterization Initiative was launched to characterize tumors and develop biomarker testing in children (631). These data will allow researchers to develop better clinical trials, identify the drivers of pediatric cancers, and support development of novel treatments for some pediatric cancers that currently lack effective treatments.

Molecularly targeted therapies have shown remarkable success for the treatment of adults with specific mutations that fuel cancer development. Many pediatric cancers exhibit the same mutations as adult cancers. However, designing clinical trials only for pediatric cancers with specific mutations is difficult because all pediatric cancers are rare. The low availability of molecularly targeted trials for pediatric patients means that targeted drugs approved to treat adult forms of cancer often do not get approved for children even when there is a strong potential for benefit. To address this issue, Congress passed key provisions of the Research to Accelerate Cures and Equity

(RACE) for Children Act as part of the FDA Reauthorization Act of 2017 to amend the Pediatric Research Equity Act (PREA). In August 2021, the RACE Act came into full effect. It requires drug manufacturers to study molecularly targeted therapeutics developed for adult patients with cancer in pediatric populations with the same mutations. In response to these provisions, FDA developed a Pediatric Molecular Target List to provide guidance to companies as they plan for new drug and biologic submissions (632). Additionally, applications submitted to FDA for therapies that meet the RACE Act criteria must have agency-approved pediatric study plans (633).

New discoveries in understanding the biology of pediatric cancers and the connection to birth defects are also being supported by The Gabriella Miller Kids First Pediatric Research Program (Kids First) at NIH. Funding for this program was established in the Gabriella Miller Kids First Research Act, passed by Congress in 2014. As of 2021, the program had completed genome sequencing of more than 20,000 participants within 44 childhood cancer and structural birth defect cohorts for whole genome sequencing and is in the process of selecting additional cohorts for 2022. More than $75 million has been invested in pediatric research through this initiative. The bipartisan Gabriella Miller Kids First Research Act 2.0 was introduced in the House in January 2021 and would redirect penalties against pharmaceutical, cosmetic, supplement, and medical device companies for specified violations to the Kids First program, which is part of the NIH Common Fund. NIH would make allocations from this fund to support lifesaving pediatric research that does not duplicate existing activities.

The central sources of health insurance coverage for more than half of the children in the United States are Medicaid and the Children's Health Insurance Program (CHIP) (634,635). Coverage is limited to providers in the child's home state. If out-of-state care is necessary for treatment, the health care provider and his or her team are required to undergo screening and enrollment within the Medicaid program in the child's home state. In addition to funding research to identify novel treatments for pediatric cancers, it is imperative for Congress to reduce the regulatory hurdles for eligible health care providers to treat children enrolled in Medicaid or CHIP across state lines. The Accelerating Kids' Access to Care Act would improve access to time-sensitive care by allowing eligible out-of-state providers to enroll in multiple state Medicaid programs without undergoing additional state-by-state screening.

Building Health Equity by Addressing Cancer Disparities

As described in the *AACR Cancer Disparities Progress Report 2022* and discussed by **Congresswoman Nikema Williams** (see p. 136), systemic disadvantages greatly contribute to poorer health outcomes for medically underserved populations. Centuries of policies that restrict housing, educational, and employment opportunities for racial and ethnic minorities have led to lower health insurance coverage rates, lower utilization of preventive health services, poor nutrition, and inadequate access to quality health care. Additionally, the underrepresentation of high-quality health care facilities in low-income neighborhoods and rural communities results in a lower quality of care even for those who can afford it. Reducing cancer health disparities will require a long-term, multipronged approach that supports individuals, communities, health care centers, and federal agencies, as well as local, tribal, and state governments. Recent policy developments related to cancer screening, clinical trial participation, nutrition, and health insurance have demonstrated that progress in addressing cancer health disparities is occurring.

Routine cancer screenings are necessary to detect precancerous lesions as early as possible in cancer development; however, variability along the cancer screening continuum contributes to cancer health disparities. In 2021, USPSTF broadened lung cancer screening requirements and eligibility, reducing previously identified disparities (636). Unfortunately, follow-up care is less likely to occur in minority populations for many reasons, including being uninsured or underinsured, decreased access to care, health care system bias, and miscommunication with health care providers (270). To address the health care needs of medically underserved populations, the Affordable Care Act provided states the option to expand Medicaid coverage to families earning 138 percent of the federal poverty line or less. In June 2022, the North Carolina Senate passed House Bill 149 that would expand Medicaid no later than July 2023 (637). If House Bill 149 passes the North Carolina House of Representatives and is signed into law, North Carolina will join 38 other states (and Washington, DC) in having expanded Medicaid coverage (638). Uninsured rates in those states have decreased by nearly half in states that have expanded Medicaid compared to those that have not (638). Medicaid expansion has been particularly beneficial for young adult survivors of cancer (639,640), who have seen dramatic increases in the ability to afford health care and are therefore less likely to skip medications or delay refills.

Food security—having reliable access to affordable and nutritious food—is instrumental to cancer treatment adherence and survival (641). The United States Department of Agriculture has two categories for food insecurity: low and very low. Low food security is reported reduced quality, variety, or desirability of diet without any indication of decreased food intake. Very low food security is a disruption of eating patterns with reduced food intake (642,643). Low food security can contribute to obesity, a known risk factor for many different cancers (644). Very low food security is a gap in navigating cancer management as patients with cancer and survivors of cancer may be without reliable access to a sufficient quantity of affordable, nutritious food (645). Addressing the nutritional needs of patients with cancer and survivors has the potential to decrease cancer disparities and promote healthy outcomes. One of the encouraging efforts from CDC is the Racial and Ethnic Approaches to Community Health initiative (646). This program funds local, culturally appropriate public health efforts that promote reaching one's full health potential. That includes promoting exercise and ensuring underserved individuals have options for good nutrition across their lifespan.

Continued on page 136

The Honorable Nikema Williams

What has been your personal experience with cancer?

When my mother was 46, she was diagnosed with young-onset colorectal cancer. If it wasn't hard enough caring for my mama as she fought cancer, I also had to fight the insurance companies as they tried to deny my mom the coverage she was due.

She died at age 51, and I learned a hard truth: health care in America is not a human right. There are two health care systems in our country—one for those who have access to preventive services and quality treatment, and one for everyone else.

Nowhere is this clearer than in the disparities that exist in cancer outcomes. Black Americans have the highest death rate and shortest survival of any racial and ethnic group for most cancers. We must demand better.

I also take every birthday very seriously. I lost my mom when she was way too young. She should have celebrated many more birthdays and you never know how many you're going to get.

Has that personal experience shaped your approach to health policy and the importance of funding for cancer screening, prevention, and research?

Like too many Black Americans, I know the failures of our health care system because my family has lived them. Socioeconomic disparities, lack of medical coverage, barriers to early detection and screening, and unequal access to improvements in cancer treatments are obstacles that are taking the lives of Black Americans. There may also be biological differences that underlie these health disparities, and we need more research to foster better understanding that could lead to improved detection and treatment.

Even taking a step back from cancer, Black communities have the worst health outcomes and disparities across the board. While we must increase funding for cancer screening, prevention, and research, we must take a holistic look at our health care system and take steps to close all of our health disparities.

Which policy priorities or legislative efforts do you share that would fuel better prevention, detection, and treatment of cancer?

First things first, we need to get missed cancer screenings back on the books.

According to a January 2022 survey from the Prevent Cancer Foundation, half of Americans who had a scheduled in-person medical appointment, postponed, missed, or canceled one or more of these appointments. Three out of five Americans are not getting their recommended cancer screenings and three in 10 are not aware of which screenings they should be getting.

Y'all, that's 9.5 million canceled or postponed screenings.

We must make cancer screenings available to everyone—no matter your ZIP Code, no matter your bank account.

Like seemingly every aspect of our health care system, cancer screenings are out of reach for too many people due to cost.

If we had Medicare for All, this wouldn't be an issue. I'm just one member of Congress so I can't make Medicare for All a reality but believe me I would if I could.

What I can do is take practical steps along the way to get people the health care and cancer screenings they need.

I'm a proud cosponsor of the Medicare Multi-Cancer Early Detection Screening Coverage Act, which expands access to coverage and payment for early detection screening tests. I also cosponsored and helped pass the Honoring our PACT Act, which helps expand access to screening and treatment for our veterans who had toxic exposures.

Because of my history with cancer, and the suffering it inflicts on millions of Americans every year, I fully support President Biden's Cancer Moonshot. I'm also not going to give up on working to get Medicare for All so that we can finally reduce our country's health inequities. For now though, let's work to get all cancer screenings back on the books and make cancer screenings more accessible. Without these two pieces, a cure for cancer will remain as far away as the moon.

What is your message to the scientists and physicians working to make progress against cancer?

Don't give up. You are helping families everywhere have many more birthdays, Christmases, graduations, and everyday moments together. You are doing some of the most important work anywhere—and I thank you for everything you do.

"What I can do is take practical steps along the way to get people the health care and cancer screenings they need."

U.S. REPRESENTATIVE • GEORGIA'S 5TH DISTRICT

Several additional initiatives organized by NIH, NCI, the National Institute on Minority Health and Health Disparities (NIMHD), and CDC are designed to address cancer disparities. For example, NIH's All of Us program aims to improve precision medicine research by building one of the largest and most diverse health databases. To date, over 400,000 people have joined the research program. The NCI Community Oncology Research Program is a national network that brings cancer clinical trials and care delivery studies to people in their own communities (647). Additionally, the NCI Center to Reduce Cancer Health Disparities supports disparities research within NCI and reinforces training a diverse cancer research workforce. NIMHD is NIH's core institute to support research on the many factors that contribute to disparate health outcomes, including socioeconomics, politics, discrimination, culture, and environment. Several NIMHD-promoted funding opportunities will support the investigation of underlying factors contributing to disparities in liver and lung cancer in medically underserved populations (648). CDC's National Program of Cancer Registries is essential for understanding the scope of cancer disparities by tracking cancer rates and incidence across the United States.

Learning from COVID-19 to Strengthen Digital Health Infrastructure for Cancer Care

A robust public health infrastructure is vital for building capacity to prevent chronic diseases, such as cancer, promote healthy living, and prepare for and respond to emergencies. Every public health service relies on basic infrastructure and staffing to understand and respond to the needs of a community. However, chronic underfunding of public health efforts has left federal, state, and local public health agencies with limited staff and obsolete technology (649, 650). Federal funds cover roughly one quarter of public health spending in the United States, while the remaining three quarters comes from state and local governments (650). Unfortunately, per capita state public health funding decreased 16 percent between 2010 and 2020 and local funding decreased 18 percent. Rural communities are especially affected by public health divestment (650,651). Public health departments have struggled to quickly hire staff and replace outdated technology (652). Challenges during the COVID-19 pandemic for cancer screening and prevention programs have clearly demonstrated that robust and sustainable investments are needed to strengthen public health infrastructure to eliminate disparities in access to cancer services (653,654).

Effective public health programs for cancer prevention depend on high-quality data to identify which communities and population groups are most impacted. However, public health data-reporting systems and quality of data collected vary greatly across geography and facility type (655,656). It is concerning that many states continue to rely on outdated fax machines to report public health data (657). Fortunately, Congress appropriated an initial $50 million for CDC Data Modernization activities in FY 2020 (658); an additional $1 billion was included in the CARES Act and the American Rescue Plan as well as $50 million in FY 2021 and $100 million in FY22 appropriations (659). These funds represent a down payment on the first ever national automated public health reporting system. This system could greatly improve the efficiency of monitoring public health issues, such as cancer incidence and risk factors like obesity, as well as support real-world evidence studies to analyze population-level efficacy of cancer treatments, screenings, and prevention programs.

The growing use of telehealth during the COVID-19 pandemic by patients with cancer has demonstrated the importance of reliable and fast Internet connections for cancer care (see sidebar on **What Is Telemedicine?**, p 114). Unfortunately, approximately 42 million Americans lack access to Internet fast enough to stream video (660). Historically marginalized urban and rural communities disproportionately experience limited access to Internet services. In FY 2020, Congress appropriated $8 billion for efforts to expand Internet and telehealth infrastructure (661). Furthermore, the 2021 Bipartisan Infrastructure law included an additional $65 billion for Internet access and to subsidize subscription costs for low-income families (662). Continued support for increased Internet access and digital public health infrastructure at the federal and local levels will be vital for addressing public health challenges.

Conclusion

The annual AACR Cancer Progress Reports over the past 12 years have documented unprecedented advances against cancer. The progress is illustrated by approvals of revolutionary anticancer treatments that have brought cures to countless patients with cancer; millions of lives that have been saved because of improvements in cancer prevention and early detection; and a consistent increase in the number of children and adults who are living longer and fuller lives after a cancer diagnosis. This twelfth edition of the Report continues the tradition of disseminating the knowledge of groundbreaking advances against cancer to the American public, policy makers, and the cancer research community.

The *AACR Cancer Progress Report 2022* highlights the continued decline in the overall cancer mortality rate that has translated into nearly 3.5 million cancer deaths avoided between 1991 and 2019. In recent years, the pace of the decline has accelerated, as reflected by a 2.3 percent decrease in cancer deaths every year between 2016 and 2019. The number of cancer survivors has increased by more than one million in just the past three years and, as of January 2022, there were more than 18 million cancer survivors living in the U.S.

The tangible progress being made against cancer is also underscored by the new precision medicine-based therapeutics that were approved during the 12 months covered by this report. Many of the newly approved therapeutics have expanded the number of treatment options for patients with cancer, while some have provided the first ever therapeutic option for certain diseases, including some difficult-to-study rare forms of cancer.

An emerging approach to cancer care is the use of combinations of two or more different types of therapeutics. During the period covered in this report, FDA approved new combinations of two radionuclides to visualize and destroy prostate cancer cells; two molecularly targeted therapeutics to treat any solid tumor with a specific genetic alteration; and two immunotherapeutics, one of which targets a novel immune checkpoint protein, to treat metastatic melanoma. Similar and several new and novel types of treatment combinations are anticipated to be approved in the coming years and will solidify the importance of combination therapy as the sixth pillar of the cancer treatment paradigm.

A new wave of scientific and technological innovation has also revealed the potential of cutting-edge tools, such as liquid biopsies and AI-driven software systems, in early detection and diagnosis of cancers. Some of these tools have been already approved by FDA, and are transforming the future of early detection, interception, diagnosis, treatment, and disease surveillance. Others, such as single-cell characterization of tumors and state-of-the-art imaging techniques, will help researchers decode some of cancer's most elusive questions, such as heterogeneity and tumor evolution and treatment resistance.

Despite the major progress that is being made against cancer, as detailed in the report, there are several areas in cancer research and patient care that need to be addressed in order to provide opportunities for further advances. As highlighted throughout the report, racial and ethnic minorities and medically underserved population groups in the U.S. continue to shoulder a disproportionate burden of cancer. The epidemic of obesity in U.S. adults and youth, and that of e-cigarette use in the U.S. youth, continue to threaten the progress made against cancer. Awareness of and adherence to routine cancer screening continue to be suboptimal. Participation and diversity in clinical trials that are reflective of the U.S. cancer burden continue to be minimal. Financial burden of a cancer diagnosis on those directly affected by it, as well as on the U.S. economy, continues to be substantial. And while cancer screening and clinical trials—both of which were severely impacted by COVID-19—are returning to prepandemic levels, the full impact of the pandemic on cancer research and patient care remains to be seen.

Based on the evidence presented in the report, AACR calls upon Congress for its resolute and trusted bipartisan support to make medical research a long-term strategic priority for our nation (see **AACR Call to Action**, p. 140). All stakeholders in the cancer care continuum, dedicated to working together to fundamentally changing the burden of cancer, can seize the unprecedented scientific opportunities that lie ahead for making strides to eradicate cancer in the U.S. and worldwide.

AACR Call to Action

The groundbreaking advances against cancer detailed in this report were made possible by the efforts of a broad coalition of researchers, clinicians, cancer survivors, patient advocates, and policy makers. Decades of investment in medical research have fueled new discoveries that made it possible to better prevent, detect, diagnose, treat, and cure many types of cancer that previously lacked effective treatment options. Because of these advances, cancer death rates in the United States have steadily declined between 1991 and 2019, translating into nearly 3.5 million cancer deaths avoided. In the last three years alone, the number of cancer survivors living in the United States has increased by more than one million, reaching more than 18 million cancer survivors in 2022. Despite this progress, not everyone has benefited equally from the advances made against cancer, and further efforts are needed to ensure equitable access to quality health care for all populations.

Cancer continues to be the second leading cause of death in the United States, thus there is an urgent need for more research to accelerate the pace of progress against this disease that touches so many lives. Remarkable bipartisan, bicameral efforts in Congress have increased NIH funding by $14.9 billion, or roughly 49 percent, from FY 2015 to FY 2022. These significant investments have made it possible for researchers to discover scientific breakthroughs against cancer and many other diseases.

AACR deeply appreciates the commitment of Congress to expediting progress against cancer and other diseases through robust funding increases for NIH, as well as its support of the critical regulatory science work at FDA and public health initiatives at CDC. These investments and initiatives will transform cancer care, increase survivorship, and maintain the United States' position as a global leader in science and cancer research.

Therefore, AACR strongly encourages Congress and stakeholders committed to eradicating cancer to:

- Continue to support robust, sustained, and predictable funding growth for NIH and NCI by providing increases to the FY 2023 base budget, including $49.1 billion in base budget authority for NIH, representing an increase of $4.1 billion, and $7.766 billion for NCI, which is an increase of $853 million and is consistent with the NCI Director's Professional Judgment Budget.
- Fully fund initiatives authorized in the 21st Century Cures Act, including the National Cancer Moonshot, and ensure that Moonshot funding supplements rather than supplants NIH funding in FY 2023.
- Reauthorize the Childhood Cancer STAR Act and provide no less than $30 million for STAR Act implementation, as well as $50 million for the Childhood Cancer Data Initiative, which seeks to better understand cancer biology specific to pediatric patients and improve prevention, treatment, quality of life, and survivorship.
- Invest in vital initiatives of the CDC Division of Cancer Prevention and Control by providing at least $462.6 million to support comprehensive cancer control, central cancer registries, and screening and public awareness programs for specific cancers.
- Increase funding for FDA's critical regulatory science initiatives that advance the development and regulation of oncology products, by providing an increase of at least $318 million, for a total of $3.653 billion in discretionary budget authority in FY 2023, as recommended in President Biden's budget.
- Ensure that patients with cancer have equitable access to quality, affordable health care by expanding Medicaid and enacting the Accelerating Kids' Access to Care Act, which would reduce barriers to care for children on Medicaid who receive specialist care from an out-of-state pediatric provider.
- Increase participation and diversity of cancer clinical trials by reducing barriers for patient enrollment and encouraging diverse representation in clinical trials, as contained in the Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, respectively.
- Encourage research institutions to recruit, support, and retain a robust cancer research workforce that reflects the diversity of our society, and support NCI initiatives such as the NCI Equity and Inclusion Program that strive to build a more inclusive and equitable workforce and markedly reduce cancer disparities.
- Reduce cancer incidence and mortality by addressing nicotine addiction through expanded coverage of tobacco cessation services, removing flavored tobacco products including menthol from the market, and limiting nicotine concentration in tobacco products.
- Expand tax policies to encourage philanthropic giving so that nonprofit cancer research organizations can continue to fund high-risk, high-reward research proposals and accelerate the discovery of new treatments and cures.

The items contained in AACR Call to Action would fuel innovation and usher in a new era of cancer science, reduce cancer disparities, improve cancer prevention and detection, and bring lifesaving cures to millions of people whose lives are touched by cancer.

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Glossary*

A

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.

B

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

B-cell maturation antigen (BCMA) A receptor that plays an important role in regulating B-cell proliferation and survival. BCMA is expressed on the cell membrane of normal and malignant plasma cells, but not other normal tissues.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Biomedical Research and Development Price Index (BRDPI) A measure of how much the National Institutes of Health budget must change to maintain purchasing power. The BRDPI is updated annually.

Bispecific antibody A type of antibody that can bind to two different antigens at the same time. Bispecific antibodies are being studied in the imaging and treatment of cancer. They are made in the laboratory.

BRCA1/2 Genes that produce proteins that are involved in repairing damaged DNA. Females who inherit certain mutations in a *BRCA1* or *BRCA2* gene are at increased risk of developing breast cancer, ovarian cancer, and some other types of cancer. Males who inherit certain BRCA1 or BRCA2 mutations are at increased risk of developing breast cancer, prostate cancer, and some other types of cancer.

Breast cancer Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

C

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.

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.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2022*. The NCI has been used as the primary source for most definitions.

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.

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.

Cytotoxic An agent or substance that is toxic to living cells.

D

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

DNA mismatch repair DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage.

E

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

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.

F

Financial toxicity A term used to describe financial problems a patient has related to the cost of cancer care.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive five years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

Food and Drug Administration (FDA) An agency in the U.S. federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. FDA also makes sure that drugs, medical devices, and equipment are safe and effective, and that blood for transfusions and transplant tissue are safe.

G

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA and most genes contain the information for making a specific protein.

Glioma A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

H

Health-related 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. Also known simply as quality of life.

HER2 A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ERBB2 and NEU.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma 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 papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also plays a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

I

Immune 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.

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.

L

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Lymphocyte-activation gene 3 (LAG-3) A cell surface molecule with diverse biologic effects on T cell function. LAG-3 binds to proteins known as MHC class II and negatively regulates proliferation, activation, and homeostasis of T cells, in a similar fashion to PD-1.

M

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.

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.

Multiple myeloma A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

N

National Cancer Institute (NCI) The largest of the 27 institutes and centers of the National Institutes of Health. NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

National Institutes of Health (NIH) A federal agency in the U.S. that conducts biomedical research in its own laboratories; supports the research of nonfederal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of research investigators; and fosters communication of medical information.

Non-Hodgkin lymphoma A term for a large group of cancers that arise in B cells or T cells. Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Cutaneous T-cell lymphoma is one example of a T-cell non-Hodgkin lymphoma.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

O

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

P

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.

PEComa A family of rare tumors that form in the soft tissues of the stomach, intestines, lungs, female reproductive organs, and genitourinary organs. Most PEComas are benign (not cancer). They often occur in children with an inherited condition called tuberous sclerosis. Also called perivascular epithelioid cell tumor.

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.

R

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radionuclide Also called radioisotope, a radionuclide is an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. In cancer medicine, radionuclides are used in diagnostic tests to detect the spread of cancer using imaging as well as in therapeutics, called radiopharmaceuticals, to treat cancer.

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Renal cell carcinoma The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

S

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.

T

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Theragnostics Also called theranostics, theragnostics is a treatment approach in which cancer is visualized by positron emission tomography (PET) or computer tomography (CT) imaging using molecules that are linked to weak radionuclides and bind to specific proteins on the surface of cancer cells. Once the presence of cancer is confirmed, the same targeting agents—labeled with more potent radioactive compounds—are then used to kill cancer cells.

Treatment resistance The failure of cancer cells to respond to a treatment used to kill or weaken them. The cells may be resistant at the beginning of treatment or may become resistant after being exposed to the treatment.

Triple-negative breast cancer A type of breast cancer in which the cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative, PR-negative, HER2-negative breast cancer.

Tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

Tumor microenvironment The cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

U

Uveal melanoma A rare cancer that begins in the cells that make the dark-colored pigment, called melanin, in the uvea or uveal tract of the eye.

V

Vaccine A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

von Hippel-Lindau syndrome (VHL) A rare, inherited disorder that causes tumors and cysts to grow in certain parts of the body, including the brain, spinal cord, eyes, inner ear, adrenal glands, pancreas, kidney, and reproductive tract. Individuals with VHL syndrome have an increased risk of certain types of cancer, especially kidney cancer and pancreatic cancer.

W

Waldenström macroglobulinemia A slow-growing type of non-Hodgkin lymphoma marked by abnormal levels of IgM antibodies in the blood and an enlarged liver, spleen, or lymph nodes. Also called lymphoplasmacytic lymphoma.

Appendix

SUPPLEMENTAL TABLE 1

Surgeries for the Prevention of Cancer

Genetic Mutation	Cancer	Technique	Removes
APC	Colon cancer	Colectomy	Colon/large intestine
BRCA1 or *BRCA2*	Breast and ovarian cancers	Mastectomy and salpingo-oophorectomy	Breasts, and ovaries and fallopian tubes
CDH1	Breast and stomach cancers	Mastectomy and gastrectomy	Breast and stomach
Mutations associated with Lynch syndrome	Colon, endometrial, and ovarian cancers	Colectomy, hysterectomy, and salpingo-oophorectomy	Colon/large intestine, uterus, and ovaries and fallopian tubes
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

Adapted from (21).

SUPPLEMENTAL TABLE 2

Newly FDA-approved Anticancer Agents: August 1, 2021–July 31, 2022

Type of Treatment	Generic Name	Trade Name	Approved For	Clinical Trial(s)	Formulation
Surgery, Chemotherapy, Radiotherapy	gallium Ga 68 gozetotide	Locametz	Certain type of prostate cancer	NCT03511664	
	lutetium Lu 177 vipivotide tetraxetan	Pluvicto	Certain type of prostate cancer	NCT03511664	
	pafolacianine	Cytalux	Certain type of ovarian cancer	NCT03180307	
Molecularly Targeted Therapy	asciminib	Scemblix	Certain type of leukemia	NCT03106779; NCT02081378	
	belzutifan	Welireg	Several tumors associated with the von Hippel-Lindau syndrome	NCT03401788	
	crizotinib	Xalkori	Certain type of inflammatory myofibroblastic tumors*	NCT00939770; NCT01121588	
	dabrafenib & trametinib	Tafinlar & Mekinist	Solid tumors carrying certain type of genetic mutation*	NCT02034110; NCT02465060; NCT02124772	
	ivosidenib†	Tibsovo	Certain type of bile duct cancer*	NCT02989857	
	mobocertinib†	Exkivity	Certain type of lung cancer	NCT02716116	
	rituximab	Rituxan	Certain type of lymphoma*	NCT01516580	
	sirolimus protein-bound particles	Fyarro	Certain type of perivascular epithelioid cell tumors*	NCT02494570	
	tisotumab vedotin-tftv	Tivdak	Certain type of cervical cancer	NCT03438396	
	zanubrutinib	Brukinsa	Certain type of lymphoma*	NCT03053440; NCT03846427; NCT02343120	
Immunotherapy	brexucabtagene autoleucel	Tecartus	Certain type of leukemia*	NCT02614066	
	ciltacabtagene autoleucel	Carvykti	Multiple myeloma	NCT03548207	
	dostarlimab-gxly†	Jemperli	Solid tumors with a specific genetic feature*	NCT02715284	
	relatlimab-rmbw	Opdualag	Certain type of melanoma	NCT03470922	
	tebentafusp-tebn	Kimmtrak	Certain type of ocular melanoma	NCT03070392	
	tisagenlecleucel	Kymriah	Certain type of lymphoma*	NCT03568461	

*New cancer type approved 2021–2022

†Requires a companion diagnostic

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